Seton Hall Law Review

Volume 43 | Issue 1 Article 9

1-23-2013

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Steele, Danielle L. (2013) "The "Duty of Sameness" as a Shield - Generic Drug Manufacturers' Tort Liability and the Need for Label Independence After PLIVA, Inc. v. Mensing," *Seton Hall Law Review*: Vol. 43: Iss. 1, Article 9.
Available at: http://erepository.law.shu.edu/shlr/vol43/iss1/9

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THE "DUTY OF SAMENESS" AS A SHIELD—GENERIC DRUG MANUFACTURERS' TORT LIABILITY AND THE NEED FOR LABEL INDEPENDENCE AFTER *PLIVA, INC. V. MENSING*[1]

Danielle L. Steele[*]

I. INTRODUCTION

In 2009, healthcare expenditure in the United States reached $2.5 trillion and accounted for 17.6% of the gross domestic product, with prescription-drug spending embodying approximately 10% of that amount.[2] In 2010, prescription-drug spending continued to grow, ultimately reaching $307.4 billion.[3] The President's Fiscal Budget for 2012 allocated a greater percentage of the national economy to healthcare than to any other category, including national defense and social security.[4] Given the substantial deficit in which America remains, the significance of managing healthcare outlay is irrefutable.[5]

While the increase in prescription-drug spending from 2009 to 2010 reveals undeniably significant monetary figures, the growth rate

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[1] 131 S. Ct. 2567 (2011).

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[2] *NHE Fact Sheet*, CTRS. FOR MEDICARE & MEDICAID SERVS., https://www.cms.gov/nationalhealthexpenddata/downloads/highlights.pdf (last updated June 14, 2011, 6:37 AM) (stating that in 2009 prescription-drug spending was $249 billion, approximately 10% of the $2.5 trillion spent that year).

[3] IMS INST. FOR HEALTHCARE INFORMATICS, THE USE OF MEDICINES IN THE UNITED STATES: REVIEW OF 2010, at 15 (Apr. 2011), *available at* http://www.imshealth.com/deployedfiles/ims/Global/Content/Insights/IMS%20Institute%20for%20Healthcare%20Informatics/IHII_UseOfMed_report1_.pdf.

[4] *The President's Budget for Fiscal Year 2012*, OFFICE OF MGMT. & BUDGET, http://www.whitehouse.gov/winning-the-future/interactive-budget (last visited Dec. 9, 2011) (Healthcare Percentage of Budget: 22.62%; National Defense Percentage of Budget: 19.27%; Social Security Percentage of Budget: 20.04%).

[5] CONG. BUDGET OFFICE, AN ANALYSIS OF THE PRESIDENT'S BUDGETARY PROPOSALS FOR FISCAL YEAR 2012, at 2 (Apr. 2011), *available at* http://www.cbo.gov/ftpdocs/121xx/doc12130/04-15-AnalysisPresidentsBudget.pdf (showing that the national deficit was $1.294 trillion in 2010).

was 45% less than the preceding year.[6] An abundance of plausible explanations for the decline exist, but an increase of greater than 26% in the generic drug sector undoubtedly played a substantial role in the spending reduction.[7] Specific to cost savings and accessibility in pharmaceuticals, the merits of generic prescription drugs are virtually uncontested.[8] The cost of a brand-name drug is on average 76% greater than that of its generic equivalent; government healthcare programs, private insurers, and citizens alike recognize this savings directly.[9] In a 2010 report expounding the advantages of generic drug use for Medicare prescription plan costs, the Congressional Budget Office (CBO) stated that over 90% of prescriptions written in 2007 were filled with generic drugs, where both the generic and brand-name drug were available.[10] The CBO estimated the resultant savings of such substitution in just one year to

[6] IMS INST. FOR HEALTHCARE INFORMATICS, *supra* note 3, at 4 (5.1% in 2009 compared to 2.3% in 2010). *See* Preserve Access to Affordable Generics Act, S. 27, 112th Cong. § 2(a)(5) (2011) ("Federal dollars currently account for an estimated 30[%] of the $235,000,000,000 spent on prescription drugs in 2008, and this share is expected to rise to 40[%] by 2018.").

[7] IMS INST. FOR HEALTHCARE INFORMATICS, *supra* note 3, at 6 (combining the growth of generics and authorized generics); *see infra* note 31 and accompanying text (describing authorized generics).

[8] Press Release, Generic Pharmaceutical Ass'n, Health Care Reform: One Year Later—GPhA Presses Need to Generate Savings in Health Care Reform Efforts (Mar. 23, 2011), *available at* http://www.gphaonline.org/media/press-releases/2011/health-care-reform-one-year-later-gpha-presses-need-generate-savings-healt. In a press release citing data from the Centers for Medicare and Medicaid Services the Generic Pharmaceutical Association announced that "the Medicaid generic dispensing rate now stands at 69% nationwide. Just a [one] percentage point increase in this rate would save states and the Federal Government $682 million." *Id.* This figure takes all prescriptions filled into account even where there were not generic options available. *Id.*

[9] U.S. DEP'T OF HEALTH & HUMAN SERVS., EXPANDING THE USE OF GENERIC DRUGS 5 (Dec. 1, 2010), http://aspe.hhs.gov/sp/reports/2010/GenericDrugs/ib.pdf [hereinafter EXPANDING THE USE OF GENERICS].

[10] CONG. BUDGET OFFICE, EFFECTS OF USING GENERIC DRUGS ON MEDICARE'S PRESCRIPTION DRUG SPENDING 7 (Sept. 2010), http://www.cbo.gov/ftpdocs/118xx/doc11838/09-15-PrescriptionDrugs.pdf [hereinafter EFFECTS OF USING GENERIC DRUGS]. For purposes of this Comment, a "generic" drug refers to a pharmaceutical product equivalent of the brand-name drug marketed subsequent to the innovating company's patent expiration or adjudicated invalidity; "brand-name" drugs will interchangeably be referred to as "list" drugs to maintain consistency with the U.S. Food and Drug Administration vocabulary on the topic. *See* FOOD & DRUG ADMIN., OFFICE OF GENERIC DRUGS, APPROVED DRUG PRODUCTS WITH THERAPEUTIC EQUIVALENCE EVALUATIONS, at x (32nd ed. 2012) [hereinafter THE ORANGE BOOK] *available at* http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/UCM071436.pdf.

be greater than $33 billion.[11]

Decades of legislative efforts have shaped a framework favoring entrance of generic competition to brand-name pharmaceutical products the moment patent protection expires.[12] The vast and flourishing industry of generic drug manufacturers places vital significance on the implications of a recent United States Supreme Court decision.[13] On June 23, 2011, in a five-to-four decision, the Court rendered an unanticipated interpretation of the preemption-by-impossibility doctrine, holding that manufacturers of generic prescription drugs are immune to liability for state tort failure-to-warn claims.[14] The subsequent denial of a rehearing renders the necessity of agency regulation or legislative intervention inevitable.[15]

In granting certiorari for this decision, the Court consolidated the actions of patients Gladys Mensing and Julie Demahy.[16] Pursuant to their physicians' care, Mensing and Demahy were each recipients of prescriptions for the brand-name drug Reglan to treat gastrointestinal symptoms;[17] both received the corresponding generic

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[11] EFFECTS OF USING GENERIC DRUGS, *supra* note 10 (noting that industry observers proffer a similar rate of generic use where both generic and brand-name drugs are available in the private sector); *see also* Doug Long, VP Industry Relations, IMS, Presented to NCPO: *The US Pharmaceutical Market: Trends, Issues, & Outlook*, slide 27 (Jan. 7, 2011), *available at* http://ncpo.hdma.net/pdfs/long.pdf (disregarding the availability of a generic alternative, 73.6% of all prescriptions were filled with generics as of September 2010).

[12] *See* H.R. REP. No. 98-857, pt. 1 (1984) [hereinafter Hatch-Waxman Amendments], for the hearings on the Drug Price Competition and Patent Term Restoration Act. *See generally*, The Assoc. Press, *A Historical Look at Healthcare Legislation*, THE BOSTON GLOBE, Mar. 21, 2010, http://www.boston.com/news/nation/washington/articles/2010/03/21/a_historical_look_at_health_care_legislation (providing a timeline of centuries of healthcare legislation).

[13] EFFECTS OF USING GENERIC DRUGS., *supra* note 10, at 18 ("Drugs accounting for another $43 billion in U.S. retail sales, representing a further 21[%] of the U.S. retail market in 2007, will be subject to first time generic entry during 2010 through 2012.").

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

[15] *Mensing*, 131 S. Ct. 2567, *reh'g denied*, 80 U.S.L.W. 3078 (2011).

[16] Demahy v. Actavis, Inc., 593 F.3d 428 (5th Cir. 2010), *cert. granted*, 131 S. Ct. 817 (2010), *reh'g denied*, 132 S. Ct. 56 (2011), and *rev'd sub nom.* PLIVA, Inc. v. Mensing, 131 S. Ct. 2567, *reh'g denied*, 132 S. Ct. 55 (2011);
Mensing v. Wyeth, Inc., 588 F.3d 603 (8th Cir. 2009), *rev'd sub nom.* PLIVA, Inc. v. Mensing, 131 S. Ct. 2567 (2011).

[17] *See generally*, *Gastroparesis*, AMERICAN DIABETES ASS'N, http://www.diabetes.org/living-with-diabetes/complications/gastroparesis.html (last visited Apr. 26, 2012) (discussing gastroparesis as a condition causing delayed expulsion of food from the stomach resulting in symptoms including bloating, acid reflux and discomfort amongst others—this was Mensing's diagnosis); *Gastroesophageal Reflux Disease*, PUBMED HEALTH,

drug, metoclopramide, from their pharmacists.[18] Both patients developed tardive dyskinesia (TD)[19]—a progressive and debilitating neurological disorder—after their treatments exceeded the recommended length of therapy.[20] Mensing and Demahy brought actions in their respective state courts against the individual generic manufacturers of the metoclopramide they had received.[21] Each plaintiff alleged that long-term use of metoclopramide had caused her condition and claimed that the manufacturers were liable for, *inter alia*, failure-to-warn in accordance with state product liability laws in Minnesota and Louisiana.[22] Amidst a growing circuit split on the issue,[23] the U.S. Courts of Appeals for the Fifth and Eighth Circuits found in favor of the co-existence of state tort law with the federal prescription drug regulation and held that federal parameters did not preempt the failure-to-warn claims.[24] This Comment will develop the preceding history and judicial interpretation involved in both cases more extensively below.

The holding in *PLIVA, Inc. v. Mensing* came just two years after the U.S. Supreme Court ruled that federal regulations *do not* preempt brand-name prescription drug manufacturers' state tort liability for failure-to-warn claims.[25] In *Wyeth v. Levine*, the plaintiff, Diane Levine, suffered irreversible gangrene, and ultimately amputation of her arm, because of the method of administration used to deliver the anti-nausea drug Phenergan.[26] A Vermont jury found Wyeth, the drug manufacturer, guilty of failure-to-warn of the risks associated with the

http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0001311/ (last visited Apr. 26, 2012) (describing gastroesophageal reflux as a condition in which the contents of the stomach recede to the esophagus causing heartburn and general discomfort—this was Demahy's diagnosis).

[18] *Demahy*, 593 F.3d at 430; *Mensing*, 588 F.3d at 605.

[19] *Demahy*, 593 F.3d at 430; *Mensing*, 588 F.3d at 605.

[20] TD is an incurable condition caused almost exclusively by long-term treatment with certain medications. Patients diagnosed with TD experience sudden, uncontrollable movements of voluntary muscle groups in the face, limbs, and digits. *Tardive Dyskinesia*, TD CENTER, http://www.tardivedyskinesia.com/symptoms/ (last visited Apr. 26, 2012).

[21] *Demahy*, 593 F.3d at 430; *Mensing*, 588 F.3d at 605.

[22] *Demahy*, 593 F.3d at 430; *Mensing*, 588 F.3d at 605.

[23] *See, e.g.*, *Demahy*, 593 F.3d at 431 n.7 (providing examples of circuit court decisions on the question of federal preemption of state tort law for generic pharmaceuticals).

[24] *Mensing*, 588 F.3d at 614; *Demahy*, 593 F.3d at 449.

[25] Wyeth v. Levine, 555 U.S. 555 (2009).

[26] *Id.*

method of administration used and awarded damages.[27] The Supreme Court of Vermont upheld the outcome.[28] Subsequently, the Supreme Court's decision led to consensus among circuits that federal regulation of prescription drugs did not preempt state tort liability for failure-to-warn in the case of the brand-name drug manufacturer.[29] Less clarity emerged with regard to *Wyeth*'s application to generic pharmaceutical drug manufacturers and a split ensued amongst circuits.[30]

The precedent that the Supreme Court established in *Mensing* results in inequitable and arbitrary consequences for patients, distorts the doctrine of preemption, tips the balance of oversight between state and federal powers, misinterprets congressional intent, and impedes self-regulation; the holding compels legislative or regulatory action. To provide context, Part II of this Comment will discuss the federal regulations applicable to brand-name and generic manufacturers as well as the legislative intent underlying their promulgation. Part II will also discuss the resulting proliferation of generic prescription use and forecasts of future growth. Part III will introduce substitution laws throughout the United States that govern the practice of pharmacists filling prescriptions for brand-name drugs with generic counterparts. This part will also focus on other factors influencing increased use of generics, such as formulary coverage by private insurers, Medicare and Medicaid restrictions, and the withdrawal of brand-name drugs from the market. Additionally, Part III will address proposed and enacted healthcare reform and finally, the controversial sector of authorized generics.[31] Part IV will consider the complementary objectives of state tort law and federal regulation in the pharmaceutical industry. This part will also analyze the traditional application of implied preemption-by-impossibility, as well as the case law establishing that brand-name drug manufacturers are

[27] Levine v. Wyeth, 944 A.2d 179, 182 (Vt. 2006).

[28] *Id.*

[29] *See, e.g.*, Wimbush v. Wyeth, 619 F.3d 632, 645 (6th Cir. 2010); Hughes v. Boston Sci. Corp., 631 F.3d 762, 764 (5th Cir. 2011); Dobbs v. Wyeth Pharms., 606 F.3d 1269 (10th Cir. 2010); Mason v. SmithKline Beecham Corp., 596 F.3d 387, 393 (7th Cir. 2010); *In re* Prempro Prods. Liab. Litig., 586 F.3d 547, 563 (8th Cir. 2009).

[30] *See supra* note 23 and accompanying text.

[31] *Authorized Generics*, GENERIC PHARM. ASS'N, http://www.gphaonline.org/issues/authorized-generics (last visited Apr. 26, 2012) ("An authorized generic is the brand company's own product repackaged and marketed as a generic either through a subsidiary or third party. Brand companies generally raise the brand drug's price when the authorized generic is introduced—resulting in an even greater expense to consumers.").

not liable for tortious conduct of generic manufacturers. Part V will discuss *Mensing* in light of the preceding sections and develop the dissent authored by Justice Sotomayor. Part V will also assess several of the amicus briefs submitted to the court in *Mensing* as well as cases decided in *Mensing*'s wake. Part VI will propose a solution through either legislative action or agency regulation that places manufacturers of generic drugs in a position parallel to that of brand-name drug manufacturers with respect to label responsibility. Lastly, Part VII will conclude.

II. TRIALS, TRIBULATIONS, AND TRIUMPHS—PROGRESSION IN THE FEDERAL REGULATORY FRAMEWORK OF PHARMACEUTICAL INNOVATION

A. *The Food and Drug Administration and the Federal Food, Drug, and Cosmetic Act*

The United States has a centuries-old history of making public health and welfare a centralized undertaking, with reformations traditionally gaining momentum in times of exigency.[32] In 1906, the Food and Drug Act gave rise to the modern Food and Drug Administration (FDA) and allocated responsibility to that office for consumer protection in relation to food and drugs used in interstate commerce.[33] The limited regulatory abilities of the FDA prompted passage of the Federal Food, Drug, and Cosmetic Act (FDCA) in 1938—for the first time the federal agency maintained significant oversight of public health.[34] The legislation vested power in the FDA to control the approval and marketing of all drugs, shape the quality standards for food, and inspect factories involved in food production.[35]

At present, the FDA provides the most comprehensive framework governing public health and welfare as affected by food

[32] *Significant Dates in U.S. Food and Drug Law History*, U.S. FOOD & DRUG ADMIN., http://www.fda.gov/AboutFDA/WhatWeDo/History/Milestones/ucm128305.htm (last visited Apr. 26, 2012) (an example of legislation in response to public outcry is the Sherley Amendment of 1912. The amendment was the first to "prohibit[] labeling medicines with false therapeutic claims intended to defraud the purchaser." The Sherley Amendment followed many infant deaths attributed to "Mrs. Winslow's Soothing Syrup for teething and colicky babies, unlabeled yet laced with morphine").

[33] *History*, U.S. FOOD & DRUG ADMIN., http://www.fda.gov/AboutFDA/WhatWeDo/History/default.htm (last visited Apr. 26, 2012).

[34] *Legislation*, U.S. FOOD & DRUG ADMIN., http://www.fda.gov/RegulatoryInformation/Legislation/default.htm (last visited Apr. 26, 2012).

[35] *Id.*

and drug products in the developed world.[36] The current state of reform under the Obama Administration is responsive in part to the inequitable limitations and selective coverage practices that privatized health insurance companies use; healthcare affordability for every patient remains a driving factor.[37]

B. The Drug Price Competition and Patent Term Restoration Act

In 1984, Congress passed the Drug Price Competition and Patent Term Restoration Act; the legislation is widely known as the Hatch-Waxman Amendments to the FDCA.[38] The Hatch-Waxman Amendments comprised two titles: "The purpose of Title I of the bill [wa]s to make available more low cost generic drugs by establishing a generic drug approval procedure,"[39] while "[t]he purpose of Title II of the bill [wa]s to create a new incentive for increased expenditures for research and development . . . [through] the restoration of some

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[36] *See Regulations and Policies and Procedures for Postmarketing Surveillance Programs*, U.S. FOOD & DRUG ADMIN., http://www.fda.gov/Drugs/GuidanceCompliance RegulatoryInformation/Surveillance/ucm090394.htm (last visited Dec. 10, 2012).

> The mission of FDA is to enforce laws enacted by the U.S. Congress and regulations established by the Agency to protect the consumer's health, safety, and pocketbook. The Federal Food, Drug, and Cosmetic Act is the basic food and drug law of the U.S. With numerous amendments, it is the most extensive law of its kind in the world. The law is intended to assure consumers that foods are pure and wholesome, safe to eat, and produced under sanitary conditions; that drugs and devices are safe and effective for their intended uses; that cosmetics are safe and made from appropriate ingredients; and that all labeling and packaging is truthful, informative, and not deceptive.

Id.

> Today, the FDA regulates $1 trillion worth of products a year. It ensures the safety of all food except for meat, poultry and some egg products; ensures the safety and effectiveness of all drugs, biological products (including blood, vaccines and tissues for transplantation), medical devices, and animal drugs and feed; and makes sure that cosmetics and medical and consumer products that emit radiation do no harm.

Legislation, U.S. FOOD & DRUG ADMIN., http://www.fda.gov/RegulatoryInformation /Legislation/default.htm (last visited Dec. 10, 2012).

[37] *See The Affordable Care Act*, THE WHITE HOUSE, PRES. BARACK OBAMA, http://www.whitehouse.gov/healthreform/healthcare-overview#healthcare-menu (last visited Nov. 7, 2011) ("The Affordable Care Act, passed by Congress and signed into law by the President in March 2010, gives [patients] better health security by putting in place comprehensive health insurance reforms that hold insurance companies accountable, lower health care costs, guarantee more choice, and enhance the quality of care for all Americans.")

[38] H.R. REP. No. 98-857, pt. 1 (1984).

[39] *Id.* at 14.

of the time lost on patent life while [a pharmaceutical] product is awaiting pre-market approval."[40] The public policy purpose of Title II sought to balance the effects of Title I with various incentives for innovation; Title II has little relevance for purposes of this Comment but does bear on market factors affecting brand-name pharmaceutical pricing models. The substance of Title I will constitute the discussion of this section for background purposes.

The expiration of patent protection on pharmaceutical products provides an opportunity for competition from generic drug manufacturers to drive market factors toward reduced drug costs for the public. To further the purpose of the FDA, and of Title I of the Hatch-Waxman Amendments, legislators sought to reduce economic barriers to entry for generic pharmaceutical companies:

> The manufacturer of a pioneer drug must conduct tests on humans that show the product to be safe and effective and submit the results in a New Drug Application (NDA). A manufacturer of a generic drug must conduct tests that show the generic drug is the same as the pioneer drug and that it will be properly manufactured and labeled. This information is submitted in an Abbreviated New Drug Application (ANDA).
>
> The only difference between a NDA and an ANDA is that the generic manufacturer is not required to conduct human clinical trials. FDA considers such retesting to be unnecessary and wasteful because the drug has already been determined to be safe and effective. Moreover, such retesting is unethical because it requires that some sick patients take placebos and be denied treatment known to be effective.[41]

In 1984, the ANDA procedure was available only to generic manufacturers for drugs brought to market prior to 1962; the Hatch-Waxman Amendments extended the practice to brand-name drugs developed post-1962.[42] The stated purpose was increased availability of low-cost generic drugs, and the legislative history reveals a presumption of safety already existing in such products.

C. Bringing a Novel Drug to the Public: Rigors of the NDA

Estimates cited by the U.S. Department of Health and Human Services in 2010 placed the cost of discovering and bringing a novel

[40] *Id.*
[41] *Id.* at 16.
[42] *Id.*

branded drug to market at over a billion dollars.[43] The exorbitant cost of innovation in the pharmaceutical field is unyielding, which logically makes patent protection crucial to motivate innovation.[44] Brand-name drug pricing has consistently indicated this as manufacturers incorporate the costs of bringing new products to market in their products' prices during exclusivity.

Chapter 9 of Title 21 in the United States Code lays out the applicable federal regulations for drugs distributed in interstate commerce as overseen by the FDA.[45] The application for approval to market a novel drug is extensive, requiring:

> (A) full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use; (B) a full list of the articles used as components of such drug; (C) a full statement of the composition of such drug; (D) a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug; (E) such samples of such drug and of the articles used as components thereof as the Secretary may require; (F) specimens of the labeling proposed to be used for such drug, and (G) any assessments required under section 355c of this title.[46]

The NDA investigation requirement mandates the applicant's provision of "[a] description and analysis of each controlled clinical study pertinent to a proposed use of the drug, including the protocol and a description of the statistical analyses used to evaluate the study."[47] The applicant must further provide exhaustive detail of all experiences and observations in any aspect of drug development and ownership.[48]

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[43] EXPANDING THE USE OF GENERICS, *supra* note 9, at 4 (citation omitted).

[44] Henry Grabowski, *Patents and New Product Development in the Pharmaceutical and Biotechnology Industries*, 8 GEO. PUBLIC POL'Y REV. 2 (July 2002), *available at* http://www.dklevine.com/archive/grabow-patents.pdf ("The importance of patents to pharmaceutical innovation has been reported in several cross-industry studies by economists.").

[45] 21 U.S.C. ch. 9 (2006).

[46] 21 U.S.C. § 355(b)(1) (2006).

[47] 21 C.F.R. § 314.50(d)(5)(ii).

[48] This requires:

> A description and analysis of any other data or information relevant to an evaluation of the safety and effectiveness of the drug product obtained or otherwise received by the applicant from any source, foreign or domestic, including information derived from clinical investigations, including controlled and uncontrolled studies of uses of

Less than a single percent of compounds examined in pre-clinical trials ever make it to human examination and "[o]nly [20%] of the compounds entering clinical trials survive the development process and gain FDA approval."[49] The FDA requires extensive clinical trials that adhere to rigorous standards; according to the CBO, completion of the necessary studies followed by approval of a NDA takes over eight years on average.[50]

The FDA review of clinical studies occurs in conjunction with evaluation of the proposed labeling, which must also fulfill comprehensive requirements.[51] NDA labeling specimen requirements break down to several components, which must be adhered to rigorously.[52]

> the drug other than those proposed in the application, commercial marketing experience, reports in the scientific literature, and unpublished scientific papers.

21 C.F.R. § 314.50(d)(5)(iv).

[49] Grabowski, *supra* note 44, at 4.

[50] CONG. BUDGET OFFICE, HOW INCREASED COMPETITION FROM GENERIC DRUGS HAS AFFECTED PRICES AND RETURNS IN THE PHARMACEUTICAL INDUSTRY 17 (July 1998), http://www.cbo.gov/ftpdocs/6xx/doc655/pharm.pdf [hereinafter INCREASED COMPETITION FROM GENERICS].

[51] 21 C.F.R. § 201.57.

[52] The requirements break down as follows:

> Description: Proprietary and established name of drug; dosage form; ingredients; chemical name; and structural formula.
>
> Clinical Pharmacology: Summary of the actions of the drug in humans; in vitro and in vivo actions in animals if pertinent to human therapeutics; pharmacokinetics.
>
> Indications and Usage: Description of use of drug in the treatment, prevention, or diagnosis of a recognized disease or condition.
>
> Contraindications: Description of situations in which the drug should not be used because the risk of use clearly outweighs any possible benefit.
>
> Warnings: Description of serious adverse reactions and potential safety hazards, subsequent limitation in use, and steps that should be taken if they occur.
>
> Precautions: Information regarding any special care to be exercised for the safe and effective use of the drug. Includes general precautions and information for patients on drug interactions, carcinogenesis/mutagenesis, pregnancy rating, labor and delivery, nursing mothers, and pediatric use.
>
> Adverse Reactions: Description of undesirable effect(s) reasonably

The label, once approved, forms the basis upon which physicians rely in making their prescribing decisions for individual patients.[53] The label also provides patients with information they need to be fully informed about the drugs they are consuming and the likelihood of experiencing risks and benefits associated with such consumption. Based upon its crucial role in placing consumers on notice, the label constitutes a source of tort liability, thus providing another powerful incentive for manufacturers to provide comprehensive disclosure. Essentially, patients and physicians are the end consumers of a manufacturer's pharmaceutical product, so the manufacturer is naturally inclined to balance a desire to stay profitable with legal requirements of disclosure imposed by federal regulation and risk of tort liability.

D. Imitation is Inexpensive and Encouraged: The Ease of the Abbreviated New Drug Application

Based on the success of the Congressional actions discussed *supra*, the average cost of bringing a generic drug to market is under $2 million, less than a quarter of the average costs associated with novel drugs.[54] "In essence, imitation costs in pharmaceuticals are extremely low relative to the innovator's costs for discovering and developing a new compound."[55] A manufacturer filing an ANDA

> associated with the proper use of the drug.
>
> Drug Abuse/ Dependence: Description of types of abuse that can occur with the drug and the adverse reactions pertinent to them.
>
> Overdosage: Description of the signs, symptoms and laboratory findings of acute overdosage and the general principles of treatment.
>
> Dosage/ Administration: Recommendation for usage dose, usual dosage range, and, if appropriate, upper limit beyond which safety and effectiveness have not been established.
>
> How Supplied: Information on the available dosage forms to which the labeling applies.

Shashank Upadhye, *Abbreviated New Drug Application (ANDA) Approval Process, Labeling Review*, *in* GENERIC PHARM. PATENT & FDA LAW, § 7:9 tbl.7-3 (Feb. 2012), *available at* Westlaw GENPHARMA § 7:9.

[53] *Training and Continuing Education*, U.S. FOOD & DRUG ADMIN., http://www.fda.gov/AboutFDA/WhatWeDo/History/default.htm (last visited Dec. 11, 2012) (stating that the "primary purpose [of drug labeling] is to give healthcare professionals the information they need to prescribe drugs appropriately").

[54] EXPANDING THE USE OF GENERICS, *supra* note 9, at 4–5 (citation omitted).

[55] Grabowski, *supra* note 44, at 4.

must include information showing that the generic drug for which it seeks approval has the same active ingredients as the "listed drug" for which it claims equivalence.[56] The term "listed drug" refers to the drug "identified by the FDA as the drug product upon which an applicant relies in seeking approval of its ANDA."[57] Inactive ingredients are not required to be the same as the list drug upon which the ANDA relies.[58] The application must "identify and characterize the inactive ingredients in the proposed drug product and provide information demonstrating that such inactive ingredients do not affect the safety or efficacy of the proposed drug product."[59] The ANDA must further provide "[i]nformation to show that the route of administration, dosage form, and strength of the drug product are the same as those of the reference listed drug."[60]

In lieu of clinical trials proving safety and efficacy for the drug's intended use, the ANDA must furnish data establishing the bioequivalence of the generic drug to the list drug;[61] this standard is the driving force of generic manufacturers' cost savings in the process of bringing a drug to market.[62] The FDA does not require active ingredients to be identical for approval: "any formulations that have minor differences in composition or method of manufacture from the formulation submitted for approval, but are similar enough to be relevant to the agency's determination of bioequivalence [are

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[56] 21 U.S.C. § 355(j)(2)(A)(ii) (2006).

[57] THE ORANGE BOOK, *supra* note 10, at x.

[58] 21 C.F.R. § 210.3(b)(8) ("Inactive ingredient means any component other than an active ingredient."). *See generally* 21 C.F.R. § 210.3(b)(7) ("Active ingredient means any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure of any function of the body of man or other animals.").

[59] 21 C.F.R. § 314.94(a)(9)(ii).

[60] 21 C.F.R. § 314.94(a)(6)(i). *See generally* discussion *supra* Part II.C.

[61] 21 C.F.R. § 314.94(a)(7)(ii); *see also* 21 C.F.R. § 320.1(e).

> Bioequivalence means the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study.

Id.

[62] *Facts and Myths about Generic Drugs*, U.S. FOOD & DRUG ADMIN., http://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/UnderstandingGenericDrugs/ucm167991.htm (last visited Apr. 26, 2012) ("Generic manufacturers . . . generally do not pay for costly advertising, marketing, and promotion.").

allowable]."[63] In all applications, the generic manufacturer must certify that the drug will not violate the patent of the listed drug.[64] The imitative nature of this process drastically increases the likelihood that a generic manufacturer's product will make it to market.

Most relevant to this Comment, the ANDA must include "[a] side-by-side comparison of the applicant's proposed labeling . . . with the approved labeling for the reference listed drug."[65] Simply stated, "[l]abeling . . . proposed for the drug product must be the same as the labeling approved for the reference listed drug."[66]

> The regulations, however, do not require absolute identity with the branded label. . . . [D]ifferences may include "differences in expiration date, formulation, bioavailability, or pharmacokinetics, labeling revisions made to comply with current FDA labeling guidelines or other guidance, or omission of an indication or other aspect of labeling protected by patent or accorded exclusivity."[67]

The requirement of label mimicry is logical at the application stage because the generic applicant relies entirely on the safety and efficacy established vicariously by the list drug's trials in support of the original NDA. ANDA contenders have not conducted independent trials and have no data adhering to FDA standards of reliability.

In the event that a generic manufacturer wishes to submit an ANDA where the list drug is no longer marketed by the brand-name manufacturer, the application "must contain all evidence available to the petitioner concerning the reasons for the withdrawal from sale."[68] Upon a determination that the marketing of the drug was not discontinued for reasons associated with safety or efficacy, the ANDA will be approved relying on the NDA of the discontinued drug[69]:

> The "Discontinued Drug Product List" identifies, among other items, drug products that have been discontinued from marketing for reasons other than safety or

[63] 21 C.F.R. § 320.1(g); *see also Bioequivalence*, GENERIC PHARM. ASS'N, http://www.gphaonline.org/issues/bioequivalence (last visited Apr. 26, 2012) ("Based on FDA analysis of hundreds of bioequivalence studies, FDA has determined that small differences in blood levels—less than 4%—may exist in some cases between a brand and its generic equivalent.").

[64] 21 C.F.R. § 314.94(a)(12).

[65] 21 C.F.R. § 314.94(a)(8)(iv).

[66] *Id.*

[67] Upadhye, *supra* note 52, at § 7:9 (quoting 21 C.F.R. § 314.94(a)(8)(iv)).

[68] 21 C.F.R. § 314.122(a).

[69] 21 C.F.R. § 314.122(c).

> effectiveness. Approved ANDAs that refer to the NDAs listed in this document are unaffected by the discontinued marketing of the products subject to those NDAs. Additional ANDAs that refer to these products may also be approved by the agency if they comply with relevant legal and regulatory requirements.[70]

Brand-name manufacturers frequently withdraw products that are subject to generic competition because they are no longer profitable to maintain on the market. Once the product is removed from public access, the manufacturer has no obligation to monitor its safety, and safety will remain virtually unchanged as it pertains to that product because the drug is no longer being produced or consumed. "A third of generic drugs no longer have name-brand competitors at all," leaving consumers without brand-name options.[71] As discussed below, this also leaves the FDA as the only party capable of unilaterally changing the label. Presently, no regulations exist that alter the reporting requirements or label-updating abilities discussed below of ANDA-approved drugs that rely on withdrawn list drugs.

E. Post-Approval Safety Compliance and Mechanisms of Independent Label Modification

Safety, in terms of novel drugs, is a dynamic concept. The safety studies conducted for NDA approval exist in a vacuum; by definition, long-term safety cannot exist if a drug has not been present over an extended period of time. Furthermore, the market changes perpetually—drug interactions will continue to arise as novel compounds are invented and introduced to the public. In order to maintain current data, manufacturers of approved drugs, whether by NDA or ANDA,[72] must comply with monitoring and reporting requirements regarding the safety of the drug they market:

The manufacturer of a drug "shall promptly review all

[70] Determination that MOTRIN (Ibuprofen) Tablets and Four Other Drug Products Were Not Withdrawn From Sale for Reasons of Safety or Effectiveness, 75 Fed. Reg. 48352, 48353 (Aug. 10, 2010), *available at* http://www.gpo.gov/fdsys/pkg/FR-2010-08-10/pdf/2010-19638.pdf.

[71] Transcript of Oral Argument at 41, PLIVA, Inc. v. Mensing, 131 S. Ct. 2567 (2011) (No. 09-993), *available at* http://www.supremecourt.gov/oral_arguments /argument_transcripts/09-993.pdf.

[72] 21 C.F.R. § 314.98(a) ("[E]ach applicant having an approved abbreviated new drug application under § 314.94 that is effective shall comply with the requirements of § 314.80 regarding the reporting and recordkeeping of adverse drug experiences.").

> adverse drug experience[73] information obtained or otherwise received by the applicant from any source, foreign or domestic, including information derived from commercial marketing experience, postmarketing clinical investigations, postmarketing epidemiological/surveillance studies, reports in the scientific literature, and unpublished scientific papers."[74]

The manufacturer must also "develop written procedures for the surveillance, receipt, evaluation, and reporting of postmarketing adverse drug experiences to the FDA."[75]

Regulations mandate that "[t]he applicant . . . report to the FDA adverse drug experience information."[76] An applicant's failure to conform to the recording and reporting requirements provides the FDA grounds to "withdraw approval of the application and, thus, prohibit continued marketing of the drug product that is the subject of the application."[77] Both generic and brand-name drugs are subject to virtually identical post-market requirements; this is delineated in the regulations by referring generic drug manufacturers to the regulations pertaining to drugs approved by NDA.[78] Adverse event reporting is a critical component to the FDA's understanding of long-term safety. Although there are mechanisms for patients and physicians to make such reports directly to the FDA, manufacturers provide the vast majority of the submissions—over 96% in 2010.[79]

One of the procedures available to a drug manufacturer to effect label changes that it considers necessary based upon post-approval

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[73] Adverse drug experience is defined as:

> Any adverse event associated with the use of a drug in humans, whether or not considered drug related, including the following: An adverse event occurring in the course of the use of a drug product in professional practice; an adverse event occurring from drug overdose whether accidental or intentional; an adverse event occurring from drug abuse; an adverse event occurring from drug withdrawal; and any failure of expected pharmacological action.

21 C.F.R. § 314.80(a).

[74] 21 C.F.R. § 314.80(b); *see also* 21 C.F.R. § 314.50(d)(5)(iv) (equivalent standard promulgated for reporting in NDA).

[75] 21 C.F.R. § 314.80(b).

[76] 21 C.F.R. § 314.80(c).

[77] 21 C.F.R. § 314.80(j).

[78] 21 C.F.R. § 314.98.

[79] In 2010, the FDA received 758,890 adverse event reports. Only 28,952 came from reporting parties other than the manufacturer. *Reports Received and Reports Entered into AERS by Year*, U.S. FOOD & DRUG ADMIN., http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm070434.htm (last visited Dec. 11, 2012).

discoveries is the submission to the FDA of a supplement to the manufacturer's approved application.[80] The regulation most pertinent to this Comment applies to "moderate changes."[81] Where the manufacturer of an already approved drug finds it necessary to "add or strengthen a contraindication, warning, precaution, or adverse reaction," the manufacturer may do so without prior FDA approval so long as the agency receives notice "30 days prior to distribution of the drug."[82] The manufacturer may make changes to

> add or strengthen a statement about drug abuse, dependence, psychological effect, or overdosage; . . . add or strengthen an instruction about dosage and administration that is intended to increase the safe use of the drug product; . . . delete false, misleading, or unsupported indications for use or claims for effectiveness;

or for any other reason deemed appropriate by the FDA.[83] "The supplement must be labeled 'Supplement—Changes Being Effected.'"[84]

The Changes Being Effected (CBE) method is not available to manufacturers of generic drugs approved pursuant to an ANDA.[85] Although the regulation does not explicitly state so, the "supplements are subject to the substantive standards governing applications, so the CBE regulation must be read in conjunction with regulations pertaining specifically to generic labeling."[86] As illustrated *supra*, "[t]hose regulations require a generic drug's labeling to be the same

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[80] 21 C.F.R. § 314.70.

[81] 21 C.F.R. § 314.70(c).

[82] 21 C.F.R. § 314.70(c)(6)(iii)(A).

[83] 21 C.F.R. § 314.70(c)(6)(iii)(B)–(E). *But see* Supplemental Applications Proposing Labeling Changes for Approved Drugs, Biologics, and Medical Devices, 73 Fed. Reg. 2848-01 (Jan. 16, 2008).

> Allowing sponsors to unilaterally amend the labeling for approved products without limitation—even if done to add new warnings—would undermine the FDA approval process required by Congress. Indeed, permitting a sponsor to unilaterally rewrite the labeling for a product following FDA's approval of a product and its labeling would disrupt FDA's careful balancing of how the risks and benefits of the product should be communicated. . . . The CBE supplement procedures are narrow exceptions to this general rule.

Id.

[84] 21 C.F.R. § 314.70(c)(3).

[85] PLIVA, Inc. v. Mensing, 131 S. Ct. 2567, 2575 (2011).

[86] Brief for the United States as Amici Curiae Supporting Respondents at 13, PLIVA, Inc. v. Mensing, 131 S. Ct. 2567 (2011) (No. 09-993), 2010 WL 4339894, at *13.

as the labeling of the reference listed drug."[87]

The FDA may withdraw approval of a generic drug approved pursuant to an ANDA at any time if it is determined that the generic drug's labeling "is no longer consistent with that for the listed drug referred to in the abbreviated new drug application."[88] As such, post-approval changes made unilaterally by generic manufacturers are sufficient grounds for revocation of the FDA's authorization to market their drug. This conclusion is supported by the FDA's response to commentary reproduced in the preamble of the final adoption of the ANDA regulations:

> Two comments said the labeling provisions should be revised to permit ANDA applicants to deviate from the labeling for the reference listed drug to add contraindications, warnings, precautions, adverse reactions, and other safety-related information. One comment added that ANDA applicants should be allowed to delete some of the indications contained in the labeling for the reference listed drug.
>
> FDA disagrees with the comments. . . . ANDA product's labeling must be the same as the listed drug product's labeling because the listed drug product is the basis for ANDA approval. Consistent labeling will assure physicians, health professionals, and consumers that a generic drug is as safe and effective as its brand-name counterpart. If an ANDA applicant believes new safety information should be added to a product's labeling, it should contact FDA, and FDA will determine whether the labeling for the generic and listed drugs should be revised. After approval of an ANDA, if an ANDA holder believes that new safety information should be added, it should provide adequate supporting information to FDA, and FDA will determine whether the labeling for the generic and listed drugs should be revised.[89]

It is a well "established proposition that an agency's construction of

[87] *Id.*

[88] 21 C.F.R. § 314.150(b)(10).

[89] Abbreviated New Drug Application Regulations, 57 Fed. Reg. 17950-01, 17961 (Apr. 28, 1992) (internal citations omitted); *see also* Supplemental Application Proposing Labeling Changes for Approved Drugs, Biologics, and Medical Devices, 73 Fed. Reg. 2848-01, n.1 (Jan. 16, 2008) ("CBE changes are not available for generic drugs approved under an abbreviated new drug application under 21 U.S.C. 355(j). To the contrary, a generic drug manufacturer is required to conform to the approved labeling for the listed drug.").

its own regulations is entitled to substantial deference."[90] A reading of the FDA's response can only lead to a conclusion that the agency did not intend to make the CBE method available to generic manufacturers.

The second tool for unilateral label modification implicated in this Comment is known as the Dear Health Care Provider (DHCP) letter.[91] The DHCP letter is an efficient method by which drug manufacturers can communicate directly with prescribers to inform them of updates similar in nature to those conveyed in a CBE.[92] Where a manufacturer deems a safety update necessary, the manufacturer has the ability to send a direct communication to the relevant healthcare providers;[93] it is logical that the manufacturer would prefer this direct method of disclosure to avoid conflicting use by consumers. The federal regulation pertaining to this approach is largely related to format and does not specifically prevent use by generic manufacturers.[94] FDA regulations, however, define "mailing pieces . . . for use by medical practitioners . . . to be labeling," making the DHCP letter off-limits to generic manufacturers for purposes of

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[90] Lyng v. Payne, 476 U.S. 926, 939 (1986); *see also* 2 FEDERAL PROCEDURE § 2:386 (2012).

> It is presumed that Congress intended to invest interpretive power in the administrative actor in the best position to develop historical familiarity and policy-making expertise. Because applying an agency's regulation to complex or changing circumstances calls upon the agency's unique expertise and policy-making prerogatives, it is presumed that the agency's power authoritatively to interpret its own regulations is a component of the agency's delegated law-making power.

2 FEDERAL PROCEDURE, *supra*.

[91] 21 C.F.R. § 200.5; *see also* U.S. FOOD & DRUG ADMIN., DEAR HEALTH CARE PROVIDER LETTERS: IMPROVING COMMC'N OF IMPORTANT SAFETY INFO. 3 (2010), *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatory Information/Guidances/UCM233769.pdf.

> In general, a DHCP letter is used to inform health care practitioners about important new information about a drug. In most cases, the new information is about an important new safety concern that could affect the decision to use a drug or require some change in behavior by health care practitioners, patients, or caregivers to reduce the potential for harm from a drug.

U.S. FOOD & DRUG ADMIN., DEAR HEALTH CARE PROVIDER LETTERS: IMPROVING COMMC'N OF IMPORTANT SAFETY INFO. 3 (2010), *supra*.

[92] U.S. FOOD & DRUG ADMIN., DEAR HEALTH CARE PROVIDER LETTERS: IMPROVING COMMC'N OF IMPORTANT SAFETY INFO. 3 (2010), *supra* note 91.

[93] 21 C.F.R. § 200.5.

[94] *Id.*

consumer communication.[95]

F. Hatch-Waxman Amendments: The Triumph of Title I

The Hatch-Waxman Amendments have produced vast success in reducing both the time it takes for generic competitors of brand-name drug manufacturers to get to market and prescription drug costs for patients.

> By accelerating the approval process for a generic drug and also allowing its producer to begin clinical tests before the patent on the innovator drug had expired, the Hatch-Waxman Act reduced the average delay between patent expiration and generic entry from more than three years to less than three months for top-selling drugs.[96]

Prior to the enactment of the Hatch-Waxman Amendments "[i]n 1983, only 35[%] of the top-selling drugs with expired patents (excluding antibiotics and drugs approved before 1962) had generic versions available. Today, nearly all do."[97] IMS, a pharmaceutical industry leader in data collection and analysis, asserts that from 2004 to 2010, generic share of total prescriptions in America increased from 51% of the market to 74%.[98] "The market available for direct generic substitution has increased from 61% of total scripts to 81%" and "[p]rice competition within the generic market is intense . . . contributing to the decline in average therapy costs."[99] A 2007 year-end review published by the Generic Pharmaceutical Association printed a Q & A with the organization's President and CEO:

> Clearly, there is confidence in the use of generic medicines and the recognition of the benefits they provide. Every day, more consumers are realizing that generics provide the same medicine and the same results as brands, but at a significantly lower cost. [Consumers] can also be assured that generics are just as safe as brands because they are held to the same high FDA approval standards.[100]

The final sentence of this statement is particularly pertinent to this

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[95] 21 C.F.R. § 202.1(l)(2).

[96] *See* INCREASED COMPETITION FROM GENERICS, *supra* note 50, at xiii.

[97] *Id.*

[98] *The US Pharmaceutical Market: Trends, Issues, & Outlook*, *supra* note 11, at slide 29.

[99] *Id.*

[100] KATHLEEN JAEGER, PRESIDENT AND CEO, GPHA, GENERICS: THE RIGHT CHOICE FOR BETTER HEALTH 6 (2008) *available at* http://www.gphaonline.org/sites/default/files/annual-report-2008.pdf.

Comment. Safety extends beyond approval and the extent of clarity and completeness in a warning label weighs heavily toward consumer perception of safety.

In addition to significantly reducing the consumer price for drugs upon the expiration of their patent, the Hatch-Waxman Amendments have virtually eliminated the delay between a patent's ceased validity and the time elapsed before generic versions of the drug enter the market; "most first generics are available when the patent expires."[101] It is common practice for "generic drug manufacturers [to] submit applications to the FDA in advance of patent expiration or in anticipation of resolution of a patent dispute."[102] Generic applications inundate the FDA at present, thus "[t]o speed generic approvals, FDA . . . requested authority to collect user fees for the review of generic drugs in the FY2011 President's Budget."[103] The FDA, to supplement its resources in the drug approval process, leverages user fees on new drug applicants as authorized by the Prescription Drug User Fee Amendments of 2007.[104] This desire to expand user fees to generic manufacturers reveals agency willingness to increase generic manufacturer costs in some areas.

The ANDA procedure that the Hatch-Waxman Amendments created in 1984 remains substantially unchanged from its original format as it pertains to this Comment.

III. NON-REGULATORY FACTORS DRIVING EXPONENTIAL GROWTH IN THE GENERIC SECTOR

In conjunction with federal legislative emphasis on generic drug availability, states and private companies have taken aggressive action to increase the utilization of generic drugs. Pharmaceutical substitution of generic equivalents for brand-name drugs began as a discretionary practice but is now a practice regulated state-by-state that influences prescription volume exponentially.[105] Private health insurers also aim to capitalize on the savings that generic prescriptions provide and do so through patient benefit

[101] *See* EXPANDING THE USE OF GENERICS, *supra* note 9, at 10.
[102] *Id.*
[103] *Id.*
[104] Prescription Drug User Fee Rates for Fiscal Year 2012, 76 Fed. Reg. 147, 45831 (Aug. 1, 2011), *available at* http://www.gpo.gov/fdsys/pkg/FR-2011-08-01/pdf/2011-19332.pdf.
[105] *See* discussion *infra* Part III.A.

manipulation.[106] Government-provided healthcare employs stringent policies that stimulate beneficiaries' utilization of generic prescriptions, and proposed legislation exhibits continued development of these procedures.[107] Finally, the most controversial parties to cash in on the generic market are the brand-name manufacturers themselves. Having already invested in the compound, many companies remove the brand labeling and market their original formulations as generics to take advantage of the market influence of the federal and state practices.[108]

A. *State Substitution Laws*

The substitution of generic drugs for their therapeutic equivalent[109] at the pharmacy is a common practice today; state law, not the FDA, regulates substitution.[110] These state laws are presumed to be the single largest factor contributing to the fact that "[w]ithin six months of patent loss, patients received the generic form of a molecule 80% of the time in 2010."[111] Prior to passage of the Hatch-Waxman Amendments, if a physician wrote a prescription indicating a brand-name drug, the pharmacist could not legally substitute that drug with the generic counterpart.[112] Naturally, the extra step for the pharmacist of attaining physician consent minimizes the likelihood of substitution. Just five years after the passage of the Hatch-Waxman Amendments, "the dispensing of generic drugs on 'brand-written' prescriptions rather than generically written prescriptions had become the chief source of generic drug sales through pharmacies."[113] Presently, every state has a law in place governing generic substitution of the therapeutic equivalent by pharmacists for prescriptions written for a brand-name drug.[114] At last count, fourteen states *mandate* generic substitution by pharmacists if "brand

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[106] *See* discussion *infra* Part III.B.

[107] *See* discussion *infra* Parts III.C, III.D.

[108] *See* discussion *infra* Part III.E.

[109] THE ORANGE BOOK, *supra* note 10, at vii ("Drug products are considered to be therapeutic equivalents only if they are pharmaceutical equivalents and if they can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling.").

[110] EXPANDING THE USE OF GENERICS, *supra* note 9, at 3.

[111] IMS INST. FOR HEALTHCARE INFORMATICS, *supra* note 3, at 21.

[112] INCREASED COMPETITION FROM GENERICS, *supra* note 50, at box 2.

[113] *Id.* (citing RICHARD E. CAVES, MICHAEL D. WHINSTON & MARK A. HURWITZ, *Patent Expiration, Entry, and Competition in the U.S. Pharmaceutical Industry*, *in* BROOKINGS PAPERS ON ECONOMIC ACTIVITY: MICROECONOMICS 1–66 (1991)).

[114] EXPANDING THE USE OF GENERICS, *supra* note 9, at app. A.

only" is not indicated by the prescribing physician on the prescription.[115]

Generic manufacturers especially value substitution laws because physicians consistently prescribe brand-name drugs rather than generics; this may be due to habit, corporate marketing efforts, or concern about the inactive ingredients in generics that vary from their brand-name counterparts.[116] A study conducted for a cholesterol medication revealed that "six months after patent expiration, 98[%] of . . . prescriptions were [filled with the generic equivalent] in states that did not require patient consent, while less than one third of prescriptions were filled by [the generic] in states that did require patient consent."[117] This data reveals that, when given a choice, patients have a strong preference for brand-name drugs.[118] This preference may be related to perceptions of value, safety, quality, manufacturer reputation or countless other possible considerations.

Beyond state law's influence, "pharmacists have a financial incentive to [dispense] generics, as the mark up received by pharmacies is largest for new generics."[119] The wholesale costs of generic drugs are generally lower than those of brand-name drugs, reducing stocking outlays for pharmacy owners and increasing marginal profits.[120] The pharmaceutical industry recognizes this advantage more consistently with government-sponsored health care programs, thus the current reform scheme's public mandate will increase the influence of pharmacists in the allocation of generic and brand-name prescription fulfillment.[121]

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[115] *Id.* (Florida, Hawaii, Kentucky, Maine, Massachusetts, Minnesota, Nevada, New Jersey, New York, Rhode Island, Tennessee, Vermont, Washington, and West Virginia).

[116] *Id.* at 12.

[117] *Id.* at 8.

[118] *See id.*

[119] EXPANDING THE USE OF GENERICS, *supra* note 9, at 8.

[120] INCREASED COMPETITION FROM GENERICS, *supra* note 50, at n.10.

[121] *See* John M. Coster, *Trends in Generic Drug Reimbursement in Medicaid and Medicare*, U.S. PHARM. (June 17, 2010), *available at* http://www.uspharmacist.com/content/s/127/c/21147/.

> Tens of millions of new Americans will have access to health insurance starting in 2014 through a combination of Medicaid expansions and an increase in the availability of federally sponsored private health insurance. Prescription drug coverage will be mandated as part of these new health insurance plans. This means that federally sponsored health care plans will pay for even more prescription drugs than they do now, and federal reimbursement policies will have more influence

B. Private Healthcare Payors

Private pharmaceutical benefit management companies (PBMs) are another prominent external factor on generic prescription volume. PBMs strategically manipulate pricing and coverage in order to influence patient behavior in prescription fulfillment.[122] The drug coverage that a plan provides can diminish the cost burden of brand-name drugs over the generic equivalent, leading the consumer to believe that any perceived superiority of the brand-name drug is worth the small price differential.[123] To avoid this occurrence and reduce their own costs, PBMs utilize tiered formulary coverage; tiers generally apply higher copays to brand-names than to generics, thereby encouraging patient utilization of the cheaper generic drug.[124] "An IMS National Prescription Audit shows that a typical formulary now charges $6 for generic medications, $29 for preferred branded drugs, and $40 or more for non-preferred branded drugs."[125] This price differential is likely to be substantial enough to influence the average consumer's choice. A more straightforward avenue for PBMs is brand restriction on formularies. Formularies are a list of drugs a patient can receive coverage for;[126] by excluding brand-name drugs, the PBM leaves the patient with only one alternative to the generic: to pay cash.

Additional mechanisms engaged to reduce use of more costly brand-name pharmaceuticals are deterrents aimed at the prescribing physician; two such policy requirements are prior-authorizations and step-therapy.[127] Prior-authorization mandates placed on specific drugs create a requirement for the physician to contact the PBM for approval before the patient will receive coverage of the brand-name drug in a class where a generic equivalent is available.[128] Primary care physicians frequently consult over thirty patients per day, placing their time at a premium and significantly decreasing the likelihood that they will engage in the necessary steps to obtain prior

on how generic drugs are used and how they are dispensed.

Id.

[122] INCREASED COMPETITION FROM GENERICS, *supra* note 50, at 6.

[123] *Id.* at 8–9.

[124] EFFECTS OF USING GENERIC DRUGS, *supra* note 10, at box 1.

[125] *Facts and Myths about Generic Drugs*, *supra* note 62.

[126] EXPANDING THE USE OF GENERICS, *supra* note 9, at n.5.

[127] *See* Stephan L. Burton et al., *The Ethics of Pharmaceutical Benefit Management*, 20 HEALTH AFF. 150, 151 (2001).

[128] *Id.* at n.6.

authorization.[129] Mitigating this likelihood further, patients do not frequently discover the condition of prior authorization until the patient brings the prescription to the pharmacy where the pharmacist will in turn substitute the brand name with a generic in accordance with state laws.[130] Step-therapy is basically a series of prerequisites for a brand-name drug, under which physicians are required to start with a specified drug and gradually work their way up to a drug that the PBM considers less preferable, generally for cost reasons.[131] Patients must fail to respond to the product, react negatively to the drug, or otherwise not meet the physician's goals in order to gain approval for movement from one step to the next.[132] Step-therapy is a hard stop to prior authorization in many cases, requiring prerequisite conditions before PBMs will cover a brand-name drug. On the other end of the spectrum, physicians are also frequently incentivized monetarily for their prescriptions.[133] Given the minefield of mechanisms preventing the use of brand-name drugs where generics are available, the market status of generics becomes less surprising.

C. Medicare and Medicaid

In 1994, the CBO "estimated that the purchase of generic drugs reduced the cost of prescriptions . . . by roughly $8 billion to $10 billion."[134] Preceding an expansion of prescription coverage for Medicare recipients in 2007, the Inspector General issued an executive summary of the findings of a study assessing the savings recognized by the government through patients' use of generic drugs in lieu of brand-name drugs:

> Under Part D, plans have broad discretion to design plan benefits and develop their drug utilization management tools. The cost of the Part D prescription drug program for 2006 was lower than the original estimate of $59 billion, and future cost estimates have also been reduced, due in part to greater than anticipated generic drug use.[135]

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[129] PHYS. PRAC., *Patients-Per-Day Norms*, Jan. 1, 2008, http://www.physicianspractice.com/qa/patients-day-norms.

[130] *See* discussion *supra* Part III.A.

[131] EXPANDING THE USE OF GENERICS, *supra* note 9, at n.8.

[132] *See, e.g.*, *Glossary*, BLUECROSS BLUESHIELD OF TEX., http://www.bcbstx.com/partd/2011/glossary.html (last visited Sept. 6, 2012).

[133] EXPANDING THE USE OF GENERICS, *supra* note 9, at n.7.

[134] INCREASED COMPETITION FROM GENERICS, *supra* note 50, at 13.

[135] OFFICE OF INSPECTOR GENERAL, GENERIC DRUG UTILIZATION IN THE MEDICARE PART D PROGRAM, at i (Nov. 2007), *available at* http://oig.hhs.gov/oei/reports/oei

Government Medicare and Medicaid programs recognize the cost benefits in a similar fashion to private insurers discussed in the preceding section,[136] but by nature, the patients they insure have insignificant choice in their insurance plans—Medicare and Medicaid serve the elderly and the poor.[137] Characteristics that qualify them for the medical coverage they receive also make them less capable of absorbing drastic medical harm that will go uncompensated by generic manufacturers based on the current preemption of state tort liability, discussed *infra*.

In 2007, Medicare Part D, the prescription-drug benefit plan under Medicare, saw 90% of prescriptions written for brand-name drugs with generic counterparts filled with the generic option.[138] According to the CBO, "[t]hat figure reflects the strong financial incentives for . . . enrollees to use generics when available."[139] Most recently, 2010 data reveals clear incentive for maintaining growth in the use of generics; "Medicaid paid on average approximately $200 for each monthly brand prescription, compared to just $20 for a month's prescription in the generic version. . . . By increasing generic utilization in Medicaid by just one percentage point, the government and taxpayers would save more than $500 million each year."[140] These patient populations are likely to see dramatic impact stemming from the holding in *Mensing*.

D. *Proposed and Enacted Legislation Favoring Generics*

Present reform of healthcare maintains similar goals to those perpetually sought by the FDA in more modern actions: affordability and availability. While the costs of expanding general public coverage are high,[141] this is inevitably offset by the FDA's centralized guidance of patients' drug choices to generics:

-05-07-00130.pdf.

[136] *Id.* at iii.

[137] CTRS. FOR MEDICARE & MEDICAID SERVS., http://www.cms.gov (last visited Jan. 16, 2012).

[138] EFFECTS OF USING GENERIC DRUGS, *supra* note 10, at 7.

[139] *Id.*

[140] Press Release, GPhA Commends Bipartisan Effort to Lower Health Care Costs Through Increased Use of Affordable Generic Medicines (Nov. 15, 2011), *available at* http://www.gphaonline.org/media/press-releases/2011/gpha-commends-bipartisan-effort-lower-health-care-costs-through-increased-.

[141] *See One Year Later—GPhA Presses Need to Generate Savings in Health Care Reform Efforts*, *supra* note 8 ("By lowering eligibility requirements, the ACA will add approximately 16 to 18 million new lives to the current 60 million Medicaid beneficiaries.").

> For brand-name drugs . . . plans will pay 2.5[%] of their cost in 2013, increasing to 25[%] by 2020 and beyond. For generic drugs purchased in that spending range, plans will pay 7[%] of the cost in 2011; that coverage will increase each year to reach a total of 75[%] by 2020.[142]

Generic expansion is not limited to drugs approved by ANDA; further reform efforts focus on extending the availability of biologics.[143] Biologics have a tendency to be exceptionally costly because they are generated from living organisms as opposed to their manufactured pharmaceutical counterparts.[144] Prior to current reform, manufacturers were not able to produce these drugs in generic form through an abbreviated process.[145] "The abbreviated pathway for approval of biosimilar biologic drugs under the Biologics Price Competition and Innovation Act of 2009, within the Patient Protection and Affordable Care Act" creates a new avenue for savings.[146] The subsequent focus of private and government pharmaceutical benefit plans will be to incentivize patients' use of the cheaper equivalent; most likely, this will be accomplished by the means discussed *supra*. Consistent with the historic promotion of affordability and availability, this act aims to reduce as many barriers to consumer-use as possible while maintaining the safety and efficacy of the regulated drugs.

E. Authorized Generics—If You Can't Beat Them, Join Them

As introduced above, the entrance of generic competition takes the vast majority of a brand-name drug manufacturer's market share in a brief time span. Exorbitant costs of innovation create a need for substantial incentive; patent protection for novel drugs provides just that, but in a capitalist market, this does not seem to be sufficient. Given the comprehensive preference for generic prescription fulfillment in the private and public sectors, it is not entirely

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[142] EFFECTS OF USING GENERIC DRUGS, *supra* note 10, at 3.

[143] Biologics represent the cutting edge of medicine, "and, in time, may offer the most effective means to treat a variety of medical illnesses and conditions that presently have no other treatments available." This line of drugs is comprised of "a wide range of products such as vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins." *What Are "Biologics" Questions and Answers*, U.S. FOOD & DRUG ADMIN., http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CBER/ucm133077.htm (last visited Feb. 12, 2012).

[144] EFFECTS OF USING GENERIC DRUGS, *supra* note 10, at 18.

[145] EXPANDING THE USE OF GENERICS, *supra* note 9, at 10.

[146] *Id.*

surprising that brand-name manufacturers have found a surreptitious way to capitalize on the self-perpetuating market of generics. In the pharmaceutical industry, the practice of brand-name manufacturers removing original packaging from their drugs and relabeling them as generics is referred to as production of an authorized generic.[147]

This practice has generated attention because it allows brand manufacturers to usurp an exclusivity period granted to the first generic manufacturer to successfully challenge a patent and come to market with a competitor.[148] This Comment does not focus on the independent complexities of this subject; instead, the existence of authorized generics is relevant because *Mensing* seems to preempt state tort liability for brand manufacturers if they market their original compound as a generic. Although the brand manufacturer would be liable for failing to warn consumers under the holding in *Wyeth*, they escape such liability through a mere package change;[149] this bizarre result cannot be an intention of the legislature. In essence, producers of a product can easily shield themselves from consumer liability and are subject to no motivating requirement to monitor safety. By this substantial loophole, all parties involved in marketing an inherently dangerous product have accountability only to maintain the status quo, regardless of what new dangers may come to their attention.[150]

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[147] *See Development & Approval Process (Drugs)*, U.S. FOOD & DRUG ADMIN., http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/ucm126389.htm#WHAT_IS_AG (last visited Jan. 18, 2012).

> An "authorized generic drug" is a listed drug as defined in § 314.3 that has been approved under subsection 505(c) of the act and is marketed, sold, or distributed directly or indirectly to retail class of trade with either labeling, packaging (other than repackaging as the listed drug in blister packs, unit doses, or similar packaging for use in institutions), product code, labeler code, trade name, or trade mark that differs from that of the listed drug.

Id.

[148] The Hatch-Waxman Amendments granted a 180-day exclusivity period to the first generic manufacturer in order to motivate prompt entrance of competition. 21 U.S.C. § 355(j)(5)(B)(iv). *See* FED. TRADE COMM'N, AUTHORIZED GENERIC DRUGS: SHORT-TERM EFFECTS AND LONG-TERM IMPACT, at i (Aug. 2011), http://www.ftc.gov/os/2011/08/2011genericdrugreport.pdf ("[C]ourts have ruled that 180-day exclusivity does not preclude a brand-name company from entering with its own generic because it already has approval for its product.").

[149] Wyeth v. Levine, 555 U.S. 555 (2009).

[150] With the exception of a footnote to the dissenting opinion in *Mensing*, the impact of that case's holding on authorized generics is not illuminated. 131 U.S. 2567, 2589 n.12 (2011) (Sotomayor, J., dissenting).

IV. CHECKS, BALANCES, AND LIABILITY

The success of the Hatch-Waxman Amendments and resultant boom in the prescription-drug market placed an enormous burden on an already beleaguered FDA. The long-standing relationship between federal regulation and state tort law is crucial to the safety of the prescription drug market. While preemption doctrine is implicated in considering federal regulation of consumer products as it impacts public health in the case at bar, it substantially hinders one underlying policy of all FDA legislation—safety. This Part establishes several supporting reasons for this assertion.

A. *The FDA's Burden*

Based on the FDA's inception and development through present day, it is arguable that its most significant underlying policy is that of safety in products that members of the public consume. Within the FDA, the Office of Surveillance and Epidemiology (OSE) and the Office of New Drugs (OND) equally share the role of post-approval safety oversight,[151] both operating under the Center for Drug Evaluation and Research (CDER).[152] Within OSE, there are five divisions, three of which focus on post-approval safety.[153] Two Divisions of Pharmacovigilance "detect and assess safety signals for all marketed drug products," and the Division of Epidemiology functions to "evaluate various postmarketing surveillance tools that may be incorporated into risk management strategies."[154] In a recently published performance self-evaluation, the FDA noted that "the number of generic applications submitted to CDER's generic drug program has grown considerably over the past decade—nearly three-fold since 2001—outpacing the growth in program personnel."[155]

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[151] John Jenkins, Gerald Del Pan & Janet Woodcock, *Memorandum of Agreement Between the [OND] and the [OSE] in the [CDER]*, *available at* http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM111520.pdf. It is unclear, however, whether this division of responsibility has been updated despite its pre-determined expiration on June 16, 2010.

[152] *Office of Surveillance and Epidemiology*, U.S. FOOD & DRUG ADMIN., http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm106491.htm (last visited Feb. 12, 2012).

[153] *Office of Surveillance and Epidemiology (OSE)-Divisions*, U.S. FOOD & DRUG ADMIN., http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm169536.htm (last visited Feb. 12, 2012).

[154] *Id.*

[155] DEP'T OF HEALTH & HUMAN SERVS., FY 2012 ONLINE PERFORMANCE APPENDIX 1,

In a report requested by the United States Senate Committee on Finance, the United States Government Accountability Office (GAO) made reference to over *thirty years* of "[c]oncerns about the FDA's management of safety issues for drugs approved for marketing."[156] In expanding on this unremitting issue, the GAO revisited a 2006 report where it found that: "OSE management had not effectively overseen postmarket drug safety and lacked systematic information;" the FDA routinely failed to track "progression of postmarketing studies that FDA had requested;" and that the "FDA faced constraints in its access to data that allow[s] it to monitor the safety of marketed drugs . . . [and] limited resources for staff training and supportive technology."[157] The GAO report noted that the FDA's workload continuously increases as they take on new responsibilities by legislation and in 2009, they continued to be understaffed in the area of postmarket drug safety.[158] Although regulations require that adverse events are reported and compiled in a central location for the purpose of monitoring safety, the utilization of this data is subject to doubt—OSE staff members reported to the GAO that "workload

available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/BudgetReports/UCM242730.pdf.

[156] U.S. GOV'T ACCOUNTABILITY OFFICE, GAO-10-68, FDA HAS BEGUN EFFORTS TO ENHANCE POSTMARKET SAFETY, BUT ADDITIONAL ACTIONS ARE NEEDED 1 (2009) [hereinafter POSTMARKET DRUG SAFETY], *available at* http://www.gao.gov/new.items/d1068.pdf. This is only one of multiple studies revealing the inability of the FDA to sufficiently monitor the safety of pharmaceutical drugs over a lifespan of market availability. *See also* BOARD ON POPULATION HEALTH AND PUBLIC HEALTH PRACTICE, THE FUTURE OF DRUG SAFETY: PROMOTING AND PROTECTING THE HEALTH OF THE PUBLIC 193–94 (2007), *available at* http://www.nap.edu/openbook.php?record_id=11750&page=R1.

> There is widespread agreement that resources for postmarketing drug safety work are especially inadequate and that resource limitations have hobbled the [FDA's] ability to improve and expand this essential component of its mission. Continued resource shortages will impede the agency's ability to use new and future scientific and technological advances in drug research across the lifecycle. In particular, the limited resources could impede the agency's ability to detect risks of new drugs in a timely fashion, analyze emerging drug safety data, and effectively communicate that information to the public.

BOARD ON POPULATION HEALTH AND PUBLIC HEALTH PRACTICE, THE FUTURE OF DRUG SAFETY: PROMOTING AND PROTECTING THE HEALTH OF THE PUBLIC 193–94 (2007), *supra*.

[157] POSTMARKET DRUG SAFETY, *supra* note 156, at 10–11.

[158] *Id.* at 31 (In a survey of OSE and OND staff members "[60%] . . . of the employees said that they either were not able to meet their postmarket drug safety responsibilities during an average workweek or were only able to meet these responsibilities by working overtime.").

demands prevent them from reviewing these reports."[159] The report estimated that the OSE would need to more than double the size of its current staff in order to adequately monitor postmarket safety.[160] Even where a budget for staff is allocated, the FDA has been unable to fill vacancies that account for half of the positions established for drug safety experts over several consecutive years.[161]

In February 2011, the GAO returned to the FDA to assess progress in resolving the "high-risk" issues noted in the 2009 report.[162] The report enumerated almost identical concerns to the 2006 and 2009 issues, adding that "FDA staff have expressed concern about their ability to meet a growing postmarket workload, with some maintaining that their premarket responsibilities are considered a higher priority."[163] Premarket safety is based on the trials required for a NDA; these trials are typically comprised of a small subset of "the population that will ultimately use the drug. Patients typically receive the drug over a short duration. Elderly persons, pregnant women, and patients who have other medical problems may be excluded, thus enrolled patients may not reflect the patients who will take the drug."[164] A perceived focus on premarket safety is exceptionally alarming given the inherent weaknesses of clinical trials for establishing safety prior to approval.

B. *State Tort Failure-to-Warn Claims*

The FDA's responsibility for drug oversight includes monitoring "the 11,000 drugs on the market,"[165] while expediting approval of new drug applications in under-funded, under-staffed circumstances. The need for tort liability to inspire self-regulation by manufacturers in a complementary fashion is self-evident. The FDA itself has "recognize[d] that product liability plays an important role in consumer protection."[166] The Supreme Court has also expressed the view that "obligation to pay compensation can be, indeed is designed to be, a potent method of governing conduct."[167] Preemption of state

[159] *Id.* at 33.
[160] *Id.* at 34.
[161] *Id.* at 38.
[162] U.S. GOV'T ACCOUNTABILITY OFFICE, GAO-11-278, HIGH-RISK SERIES 115 (1998).
[163] *Id.* at 116–17.
[164] POSTMARKET DRUG SAFETY, *supra* note 156, at 9.
[165] Wyeth v. Levine, 555 U.S. 555, 578 (2009).
[166] Protecting the Identities of Reporters of Adverse Events and Patients [and] Preemption of Disclosure Rules, 59 Fed. Reg. 3944-01, 3948 (Jan. 27, 1994).
[167] Medtronic, Inc. v. Lohr, 518 U.S. 470, 510 (1996) (O'Connor, J., concurring

tort law in the context of pharmaceutical products emphasizes the FDA's history of inadequacy in the realm of post-approval safety updates.[168] The holding of *Wyeth*, discussed *infra*, enables plaintiffs to recover damages if they can prove that a manufacturer of a brand-name pharmaceutical product acquired knowledge of a danger posed by their products, but not adequately disclosed by their labels, *after* obtaining FDA approval.[169]

Allegations of state tort law violations are generally drawn from the Restatement (Second) of Torts.[170] The comments of the Restatement shed light upon the underlying meaning in failure to warn: "In order to prevent [a] product from being unreasonably dangerous, the seller may be required to give directions or warning, on the container, as to its use."[171] More specific to the inherently dangerous nature of pharmaceutical products, the comments elucidate reluctance to impose broad liability, but instead aim to generate consumer awareness and prevent harmful or fraudulent practices.[172]

Tort liability then, is in harmony with the FDA's goals of maintaining public safety without preventing innovation and access to beneficial drugs. The FDA has iterated this proposition:

> FDA does not believe that the evolution of state tort law will cause the development of standards that would be at odds with the agency's regulations. FDA's regulations establish

in part and dissenting in part) (quoting San Diego Bldg. Trades Council v. Garmon, 359 U.S. 236, 247 (1959)).

[168] *In re* Zyprexa Products Liability Litigation, 489 F. Supp. 2d 230 (E.D.N.Y. 2007).

[169] Wyeth v. Levine, 555 U.S. 555 (2009).

[170] RESTATEMENT (SECOND) OF TORTS § 402A (1965).

[171] *Id.* at cmt. j.

[172] *Id.* at cmt. k.

> There are some products which, in the present state of human knowledge, are quite incapable of being made safe for their intended and ordinary use. These are especially common in the field of drugs. . . . Such a product, properly prepared, and accompanied by proper directions and warning, is not defective, nor is it unreasonably dangerous. The same is true of many other drugs, vaccines, and the like, many of which for this very reason cannot legally be sold except to physicians, or under the prescription of a physician. It is also true in particular of many new or experimental drugs as to which, because of lack of time and opportunity for sufficient medical experience, there can be no assurance of safety, or perhaps even of purity of ingredients, but such experience as there is justifies the marketing and use of the drug notwithstanding a medically recognizable risk.

Id.

> the minimal standards necessary, but were not intended to preclude the states from imposing additional labeling requirements. States may authorize additional labeling but they cannot reduce, alter, or eliminate FDA-required labeling.[173]

In fact, until quite recently, the FDA had emphasized its opposition to preempting tort law with regard to drug labeling.[174] It is worth noting that the FDA's unsettled position is itself relevant to a finding of preemption, and would generally lead a court to accord the agency interpretation less weight.[175]

In cases where patients injured by generic versions of pharmaceutical products have attempted to hold the manufacturer of the reference-listed drug liable, they have been categorically unsuccessful.[176] The element of causation is only met if the injured party in a pharmaceutical products liability claim establishes that he or she has actually ingested the defendant's product.[177] This substantially increases the bearing of substitution laws and preemption in FDA regulated products; because federal law does not recognize private litigants with a right of action, consumer injuries will be borne solely by the consumer if tort law is preempted.

C. Preemption Doctrine and Healthcare

Where a conflict exists between federal and state law, courts rely on preemption doctrine to find the state law a nullity. This power inures from the Supremacy Clause of the Constitution.[178] Federal preemption is an issue that frequently comes before the U.S. Supreme Court and is contentious for what opponents see as a usurpation of state independence and what proponents see as a

[173] Prescription Drug Product Labeling [and] Medication Guide Requirements, 63 Fed. Reg. 66378-01, 66384 (Dec. 1, 1998).

[174] "FDA has determined that this proposed rule does not contain policies that have federalism implications or that preempt State law." Requirements on Content and Format of Labeling for Human Prescription Drugs and Biologics [and] Requirements for Prescription Drug Product Labels, 65 Fed. Reg. 81082, 81103 (Dec. 22, 2000).

[175] While agency consistency is a factor in a court's consideration, it does not entirely eliminate the deference they receive in such considerations. Chevron, U.S.A., Inc. v. NRDC, Inc., 467 U.S. 837, 863 (1984).

[176] *See, e.g.*, Stoddard v. Wyeth Inc., 630 F.Supp.2d 631 (E.D.N.C. 2009); Schrock v. Wyeth, Inc., 601 F.Supp.2d 1262 (W.D. Okla. 2009); Swicegood v. Pliva, Inc., 543 F.Supp.2d 1351 (N.D. Ga. 2008).

[177] Absent a duty of care to an injured party, a defendant will not be found liable for breach. Levine v. Wyeth Inc., 684 F.Supp.2d 1338 (M.D. Fla. 2010).

[178] *See* U.S. CONST. art. VI, § 2.

valuable lubricant for interstate commerce.[179] The Court has established three specific grounds by which courts should find preemption of state law:

> First, Congress can define explicitly the extent to which its enactments pre-empt state law. . . . Second, in the absence of explicit statutory language, state law is pre-empted where it regulates conduct in a field that Congress intended the Federal Government to occupy exclusively. . . . Finally, state law is pre-empted to the extent that it actually conflicts with federal law. Thus, the Court has found pre-emption where it is impossible for a private party to comply with both state and federal requirements.[180]

Where preemption is not explicit, "[t]he purpose of Congress is the ultimate touchstone."[181]

In the event that federal agencies exist to oversee specific areas of interstate commerce, those agencies are on notice by Executive Order to minimize preemption of state law to the greatest extent possible.[182] State tort laws are a common area of preemptive question with respect to drugs and the FDA's oversight of them.[183] Recently, a 2008 committee report cited to extensive evidence of the FDA's acceptance of "state lawsuits as providing a valuable complement to the agency's regulation of these products. The agency has asserted that these cases help to uncover risks that are unknown to the agency at the time of approval and that they provide an important additional layer of consumer protection."[184] In addition to its supporting role as

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[179] *Regulatory Preemption: Are Federal Agencies Usurping Congressional and State Authority?: Hearing Before the S. Comm. on the Judiciary*, 110th Cong. (2007) (testimonies of Senator Patrick Leahy and Alan Untereiner), *available at* http://www.judiciary.senate.gov/hearings/testimony.cfm?id=e655f9e2809e5476862f735da12d7b7c&wit_id=e655f9e2809e5476862f735da12d7b7c-0-1 and http://www.judiciary.senate.gov/hearings/testimony.cfm?id=e655f9e2809e5476862f735da12d7b7c&wit_id=e655f9e2809e5476862f735da12d7b7c-1-2.

[180] English v. Gen. Elec. Co., 496 U.S. 72, 78–79 (1990).

[181] Medtronic, Inc. v. Lohr, 518 U.S. 470, 485 (1996).

[182] Exec. Order No. 13,132, 64 Fed. Reg. 153 (Aug. 4, 1999) ("Any regulatory preemption of State law shall be restricted to the minimum level necessary to achieve the objectives of the statute pursuant to which the regulations are promulgated.").

[183] *Regulatory Preemption: Are Federal Agencies Usurping Congressional and State Authority?: Hearing Before the S. Comm. on the Judiciary*, 110th Cong. (2007) (testimony of Senator Russ Feingold), *available at* http://www.judiciary.senate.gov/hearings/testimony.cfm?id=e655f9e2809e5476862f735da12d7b7c&wit_id=e655f9e2809e5476862f735da12d7b7c-0-2.

[184] COMMITTEE ON OVERSIGHT AND GOVERNMENT REFORM, U.S. HOUSE OF REP., MAJORITY STAFF REPORT, FDA CAREER STAFF OBJECTED TO AGENCY PREEMPTION POLICIES 1 (Oct. 2008) (Report also noted that "assertions about the ability of the drug

a negative motivator, there is a strong presumption against preemption in regulation of health and safety because of the traditional oversight by the states in this field.[185]

D. *FDA Regulation of Brand-Name Drug Manufacturers Does Not Preempt State Tort Liability*

As introduced above, *Wyeth v. Levine* involved a patient who received an injection of the brand-name drug Phenergan, an anti-nausea medication, by a method that embodied a significant risk of drastic consequences.[186] The tragic result for the patient, a professional musician, was amputation of her arm following irreversible gangrene.[187] Investigation revealed numerous missed opportunities for the offending method to be circumvented through an updated warning to the pharmaceutical product's label.[188] This case exemplifies substantial support for the key role that state tort law plays in stimulating self-regulation of pharmaceutical manufacturers. The defendant pharmaceutical company argued that the plaintiff's state tort law claims for failure-to-warn were preempted by impossibility; specifically the defendant manufacturer claimed that federal regulation prevented it from unilaterally changing its label.[189] The Court vehemently rejected this argument in a six-to-three majority opinion authored by Justice Stevens.[190]

In *Wyeth v. Levine*, the trial record revealed an example of correspondence concerning the warning section of a label between the FDA and the brand-name pharmaceutical manufacturer over a period of *seventeen years*.[191] The communication concerned the very risk that led to amputation of the plaintiff's arm, an injury that had been reported to the manufacturer over twenty times prior to the plaintiff's fate.[192] This serves as an illustration of an overtaxed regulatory agency overlooking crucial data, which had been directly reported to it, with catastrophic results.[193]

approval process to ensure accurate and up-to-date drug labels [were erroneous].").

[185] *Medtronic*, 518 U.S. at 485.

[186] Wyeth v. Levine, 555 U.S. 555 (2009).

[187] *Id.* at 559.

[188] *Id.* at 561–62.

[189] *Id.* at 562–63.

[190] *Id.* at 558.

[191] *Id.* at 561–62.

[192] *Wyeth*, 555 U.S. at 563.

[193] This case is illustrative of the inevitable oversights resulting from an overburdened FDA: Phenergan, the drug which caused Levine's injury, obtained

The *Wyeth* Court went on to discuss the "two cornerstones of our pre-emption jurisprudence."[194] To first determine Congress's intent, the Court discussed the history of the relevant federal regulation:

> As it enlarged the FDA's powers to protect the public health and assure the safety, effectiveness, and reliability of drugs, Congress took care to preserve state law. The 1962 amendments added a saving clause, indicating that a provision of state law would only be invalidated upon a direct and positive conflict with the FDCA. Consistent with that provision, state common-law suits continued unabated despite FDA regulation. . . . And when Congress enacted an express pre-emption provision for medical devices in 1976, it declined to enact such a provision for prescription drugs.[195]

The Court rejected the pharmaceutical company's argument that unilaterally altering its warning would have put it in violation of federal laws, "the very idea that the FDA would bring an enforcement action against a manufacturer for strengthening a warning pursuant to the CBE regulation is difficult to accept."[196] Wyeth's argument that the FDA was both the sole authority governing safety labeling, and shouldered complete responsibility for it, was unreliable:

> It has remained a central premise of federal drug regulation that the manufacturer bears responsibility for the content of its label at all times. It is charged both with crafting an adequate label and with ensuring that its warnings remain adequate as long as the drug is on the market. Indeed, prior to 2007, the FDA lacked the

FDA approval in 1955. In 1973 and 1976, label changes were made by Wyeth, the manufacturer of Phenergan, through supplements to their NDA. In 1981, Wyeth submitted a third supplement; discussions ensued intermittently over a span of seventeen years. In 1988, Wyeth submitted revised labeling regarding the risks accompanying a certain method of delivery; unfortunately, this was the same method of delivery that led to the amputation of Levine's arm and the injury of many other patients over several years. The FDA failed to respond to Wyeth's submission, instead instructing them to "retain verbiage in current label." *Id.* at 562 (citation omitted). In 1998, seventeen years after Wyeth's proposed label change, the FDA did respond to the supplement but still failed to address the offending method of delivery. Levine's injury was incurred in 2000, approximately two decades after the potential issue was brought to the attention of, and went unaddressed by, the FDA. This calls into question the FDA's ability to be the sole responsible entity for the safety of a market of over 11,000 generic drugs. *Id.* at 561–62.

[194] *Id.* at 565.

[195] *Id.* at 567 (internal quotations and editing omitted).

[196] *Id.* at 570.

authority to order manufacturers to revise their labels.[197]

Restricting safety oversight to the FDA alone would eviscerate the complementary nature of state tort liability for the manufacturers of pharmaceutical products.[198]

"Second, 'in all pre-emption cases, and particularly in . . . a field which the States have traditionally occupied, we start with the assumption that the historic police powers of the States were not to be superseded by the Federal Act unless that was the clear and manifest purpose of Congress.'"[199] The Court responded adversely to Wyeth's argument that the legislative intent was to create a floor and a ceiling for liability within the FDA regulations. The Court considered the absence of available remedies to patients within the FDA's regulatory framework indicative of congressional intent:

> Congress did not provide a federal remedy for consumers harmed by unsafe or ineffective drugs in the 1938 statute or in any subsequent amendment. Evidently, it determined that widely available state rights of action provided appropriate relief for injured consumers. It may also have recognized that state-law remedies further consumer protection by motivating manufacturers to produce safe and effective drugs and to give adequate warnings.[200]

The Court posited that if state tort liability had been considered an "obstacle to [Congress's] objectives, it surely would have enacted an express pre-emption provision at some point during the FDCA's 70-year history."[201] As discussed *supra*, agency regulation should avoid preempting state law to the greatest extent possible, and where

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[197] *Wyeth*, 555 U.S. at 570–71.

[198] The *Wyeth* Court emphasized the imperative role of state tort law in a rational manner:

> The FDA has limited resources to monitor the 11,000 drugs on the market, and manufacturers have superior access to information about their drugs, especially in the postmarketing phase as new risks emerge. State tort suits uncover unknown drug hazards and provide incentives for drug manufacturers to disclose safety risks promptly. They also serve a distinct compensatory function that may motivate injured persons to come forward with information. Failure-to-warn actions, in particular, lend force to the FDCA's premise that manufacturers, not the FDA, bear primary responsibility for their drug labeling at all times. Thus, the FDA long maintained that state law offers an additional, and important, layer of consumer protection that complements FDA regulation.

Wyeth, 555 U.S. at 579.

[199] *Id.* at 565 (quoting *Medtronic*, 518 U.S. at 485).

[200] *Id.* at 574 (internal citation omitted).

[201] *Id.*

unavoidable, should make preemption a clear intention. To the contrary, "despite its 1976 enactment of an express pre-emption provision for medical devices . . . (codified at 21 U.S.C. § 360k(a)), Congress has not enacted such a provision for prescription drugs."[202] The Court construed Congress's "silence on the issue, coupled with its certain awareness of the prevalence of state tort litigation, . . . [as] powerful evidence that Congress did not intend FDA oversight to be the exclusive means of ensuring drug safety and effectiveness."[203] The justification for preemption is subject to exceptionally heightened skepticism where Congress indicates its awareness of state regulation in a field of federal interest, but declines to explicitly deny their coexistence.[204]

The final contention considered by the Court concerned the FDA's preamble to a 2006 publication. The FDA's statement expressed that "failure-to-warn claims 'threaten FDA's statutorily prescribed role as the expert Federal agency responsible for

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[202] *Id.* President Barack Obama delivered a memorandum clearly stating his policy on federal preemption of state law:

> An understanding of the important role of State governments in our Federal system is reflected in longstanding practices by executive departments and agencies, which have shown respect for the traditional prerogatives of the States. . . . To ensure that executive departments and agencies include statements of preemption in regulations only when such statements have a sufficient legal basis:
>
> 1. Heads of departments and agencies should not include in regulatory preambles statements that the department or agency intends to preempt State law through the regulation except where preemption provisions are also included in the codified regulation.
>
> 2. Heads of departments and agencies should not include preemption provisions in codified regulations except where such provisions would be justified under legal principles governing preemption, including the principles [of federalism].
>
> 3. Heads of departments and agencies should review regulations issued within the past 10 years that contain statements . . . intended by the department or agency to preempt State law. . . . Where the head of a department or agency determines that [preemption is un]justified, the head of that department or agency should initiate appropriate action, which may include amendment of the relevant regulation.

Press Release, The White House, Office of the Press Sec'y, Preemption (May 20, 2009), *available at* http://www.whitehouse.gov/the-press-office/presidential-memorandum-regarding-preemption.

[203] *Wyeth*, 555 U.S. at 575.

[204] *Id.* (quoting Bonito Boats, Inc. v. Thunder Craft Boats, Inc., 489 U.S. 141, 166–67 (1989)).

evaluating and regulating drugs.'"[205] The Court made clear that it found this assertion particularly unpersuasive: "The weight we accord the agency's explanation of state law's impact on the federal scheme depends on its thoroughness, consistency, and persuasiveness."[206] The preamble statement was particularly inconsistent with the FDA's announcement that preceded the 2006 rule. "[I]n December 2000, it explained that the rule would 'not contain policies that have federalism implications or that preempt State law.'"[207]

> Further, the preamble is at odds with what evidence we have of Congress' [sic] purposes, and it reverses the FDA's own longstanding position without providing a reasoned explanation, including any discussion of how state law has interfered with the FDA's regulation of drug labeling during decades of coexistence. . . . For instance, in 1998, the FDA stated that it did "not believe that the evolution of state tort law [would] cause the development of standards that would be at odds with the agency's regulations." It further noted that, in establishing "minimal standards" for drug labels, it did not intend "to preclude the states from imposing additional labeling requirements."[208]

The Court's reasoning reflects a policy of setting reasonable expectations through consistency.

V. PREEMPTION OF STATE FAILURE-TO-WARN CLAIMS AGAINST GENERIC MANUFACTURERS

In the years following *Wyeth*, district courts consistently found that FDA regulations did not preempt the state tort law applicable to the adequacy of brand-name pharmaceutical drug label warnings. However, district courts clearly struggled with the application of the holding in *Wyeth* to generic drug manufacturers whose labels were governed by a framework materially different from that of brand-name manufacturers.[209] The Supreme Court's answer to that question in *Mensing*[210] came as a shock not only to the courts in the Fifth and Eighth Circuits, but also to four of the Justices on the bench. In a five-to-four decision, the divide between the justices was palpable.

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[205] *Id.* (quoting 71 Fed. Reg. 3922, 3935 (2006)).
[206] *Id.* at 1201.
[207] *Id.* (quoting 65 Fed. Reg. 81103 (2000)).
[208] *Id.* (quoting 63 Fed. Reg. 66378, 66384 (1998)).
[209] *See supra* note 23 and accompanying text.
[210] 131 S. Ct. 2567 (2011).

As introduced above, the cases of Mensing and Demahy ("Plaintiffs"), consolidated for purposes of certiorari, sought to answer the question "whether, and to what extent, generic manufacturers may change their labels *after* initial FDA approval."[211] The drug at issue was metoclopramide, the generic equivalent of the brand-name drug Reglan. Due to Plaintiffs' respective state substitution laws, in spite of the fact that their physicians had prescribed the brand-name drug, both received the generic alternative.[212] The FDA approved Reglan in 1980 to be marketed for the purpose of increasing the speed of food through the digestive tract; generic manufacturers entered the market five years later.[213] In 1985, the Reglan and metoclopramide labels were "modified to warn that 'tardive dyskinesia . . . may develop in patients treated with metoclopramide,' . . . and 'therapy longer than 12 weeks has not been evaluated and cannot be recommended.'"[214] In 2004, Reglan requested that the label be strengthened to state that "therapy should not exceed 12 weeks in duration."[215] Plaintiffs were prescribed the drug prior to that year. Not until 2009 did the FDA issue a black-box warning for the drug's association with tardive dyskinesia when used longer than twelve weeks.[216] The timeline of this series of events spanned nearly a quarter of a century, yet the first reports of a nexus between the side effect and the drug were reported as early as 1978.[217]

Plaintiffs asserted that the manufacturers of metoclopramide had caused each of their injuries in violation of tort laws in their respective states.[218] "They claimed that 'despite mounting evidence

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[211] *Id.* at 2574.

[212] EXPANDING THE USE OF GENERICS, *supra* note 9, at app. A (Minnesota and Louisiana, the Plaintiffs' states, are not amongst the states with the most aggressive substitution laws.).

[213] *Mensing*, 131 S. Ct. at 2572.

[214] *Id.*

[215] *Id.*

[216] *Id.* at 2573.

[217] Report of Expert Steven H. Lamm, M.D. D.T.P.H., Burnett et al, v. Wyeth Pharm. Inc., No. 3:08CV00575, 2008 WL 5653557 (N.D. Tex. Oct. 31, 2008).

[218] The decision, however, does not turn on interpretation of the state laws. *See Mensing*, 131 S. Ct. at 2573 (quoting Frey v. Montgomery Ward & Co., 258 N.W.2d 782, 788 (Minn. 1977)); Stahl v. Novartis Pharm. Corp., 283 F.3d 254, 269–70 (5th Cir. 2002)). Under Minnesota law, which applies to Mensing's lawsuit, "where the manufacturer . . . of a product has actual or constructive knowledge of danger to users, the . . . manufacturer has a duty to give warning of such dangers." *Mensing*, 131 S. Ct. at 2573. Similarly, under Louisiana law applicable to Demahy's lawsuit, "a manufacturer's duty to warn includes a duty to provide adequate instructions for safe use of a product." *Id.*

that long term metoclopramide use carries a risk of tardive dyskinesia far greater than that indicated on the label,' none of the Manufacturers had changed their labels to adequately warn of that danger."[219] The manufacturers in both cases

> urged that federal law pre-empted the state tort claims. According to the Manufacturers, federal statutes and FDA regulations required them to use the same safety and efficacy labeling as their brand-name counterparts. This means, they argued, that it was impossible to simultaneously comply with both federal law and any state tort-law duty that required them to use a different label. The Courts of Appeals for the Fifth and Eighth Circuits rejected the Manufacturers' arguments and held that Mensing and Demahy's claims were not pre-empted.[220]

According to the U.S. Supreme Court, the issue turned on "whether, and to what extent, generic manufacturers may change their labels *after* initial FDA approval."[221] Written by Justice Thomas, the majority proceeded to take the complete opposite stance to the Court's opinion in *Wyeth*, in which it found the FDA's preference to have complete dominion.[222]

Curiously, this is in spite of the FDA's submission of two separate briefs in support of respondents. The FDA's initial brief filed on November 2, 2010, recommended dismissal of certiorari. The initial discussion of congressional intent emphasized the lack of boundaries that would ensue if the Court were to find preemption:

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[219] *Mensing*, 131 S. Ct. at 2573 (quoting Mensing v. Wyeth, Inc., 588 F.3d 603, 605 (8th Cir. 2009)); *see also* Demahy v. Actavis, Inc., 593 F.3d 428, 430 (5th Cir. 2010).

[220] *Mensing*, 131 S. Ct. at 2573.

[221] *Id.* at 2574. On petition for rehearing, however, the respondents attempted to challenge this holding by logic established in *Wyeth*. According to their argument, at no point are drug manufacturers *required* to market a product they know is unsafe by state tort standards, thus giving generic manufacturers the ability to temporarily withdraw their product from the market until its label can be made sufficient; as such, the state and federal laws could have been simultaneously adhered to. Respondents' Petition for Rehearing at 3, *Mensing*, 131 S. Ct. 2567 (2011) (Nos. 09-993, 09-1039, 09-1501) (citing Justice Thomas's concurrence in Wyeth v. Levine, 555 U.S. 555, 591 (2009)).

[222] Justice Thomas in *Wyeth v. Levine*, 555 U.S. 555, 583 (2009), authored a separate concurrence that strongly emphasized his concern about the over-extension of the preemption doctrine. Justice Thomas iterated that the separation of powers made it crucial that Congress's preemptive purpose be explicit in the language of the relevant statute in order for a court to find that state laws were preempted by federal regulations. "Pre-emption must turn on whether state law conflicts with the text of the relevant federal statute or with the federal regulations authorized by that text." *Id.* at 588.

> Certainly, those Amendments were intended in part to accelerate the availability of low-cost generic drugs. "But no legislation pursues its purposes at all costs." That principle is particularly apt here because the Hatch-Waxman Amendments *amend*, and thus must be read in tandem with, the rest of the FDCA. As Wyeth explains, the FDCA's purpose is to "bolster consumer protection against harmful products," and it reflects Congress's determination that widely available state rights of action provide appropriate compensatory relief for injured consumers. Nothing in the Hatch-Waxman Amendments suggests that Congress intended to abandon those principles in the case of generic drugs.[223]

The brief went on to emphasize the Supreme Court's emphasis on certain inaction by Congress in *Wyeth*:

> Moreover, this Court reasoned in *Wyeth* that, given Congress's 1976 enactment of an express preemption provision for medical devices and its "certain awareness of the prevalence of state tort litigation," Congress "surely would have enacted an express preemption provision" if it believed that all "state-law suits posed an obstacle to its objectives." That reasoning applies here as well. Indeed, if it did not, individuals harmed by inadequately labeled generic drugs would (on petitioners' view) have no remedy, while individuals who took the same drug with the same labeling in its brand-name form would (by virtue of *Wyeth*) have a state tort remedy. "If Congress had intended to deprive injured parties of a long available form of compensation"—and to do so in such an inconsistent manner—"it surely would have expressed that intent more clearly."[224]

In spite of the deference afforded to an agency's interpretation of its regulations, the Court declined to adhere to the FDA's position.

Following grant of certiorari, the FDA filed a second brief in favor of Plaintiffs on March 2, 2011.[225] The FDA argued that the method by which the drug had gained approval was not controlling

[223] Brief for the United States as Amici Curiae Supporting Respondents, PLIVA, Inc. v. Mensing, 131 S. Ct. 2567 (2011) (Nos. 09-993, 09-1039), 2010 WL 4339894, at *20-21 [hereinafter *First Brief for the United States*] (citing Dolan v. U.S., 130 S. Ct. 2533, 2547 (2010)).

[224] *Id.* at *21 (citing *Wyeth*, 555 U.S. at 575).

[225] Brief for the United States as Amici Curiae Supporting Respondents, PLIVA, Inc. v. Mensing, 131 S. Ct. 2567 (2011) (Nos. 09-0993, 09-1039, 09-1501), 2011 WL 741927 [hereinafter *Second Brief for the United States*].

in terms of the manufacturers' responsibility for updating their labels to conform to safety requirements.[226] The FDA further asserted that finding preemption would capriciously allow manufacturers to avoid such responsibilities and arbitrarily deny relief to injured patients.[227] Although there is substantial deference given to the FDA's interpretation of its regulations, the Court clarified here that courts "do not defer to an agency's ultimate conclusion about whether state law should be pre-empted."[228]

In spite of the FDA's arguments, the Court found that the FDA regulations required the drug manufacturer of an ANDA-approved product to maintain an identical label to the reference-listed drug for which it was approved as a generic equivalent.[229] In assessing the CBE method available to drug manufacturers to unilaterally alter labels for the purpose of increasing drug warnings, the majority found that the generic manufacturers' necessary uniformity with the list drug foreclosed their ability to unilaterally do so, even if it was necessary. The majority made a similar finding in reference to other tools, such as the DHCP letter, available to brand-name drug manufacturers where urgency necessitates a label change in the absence of FDA approval beforehand.[230] If the generic drug changed its warning label

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[226] *Id.* at *24.

[227] *Id.* at *26.

> When, as here, federal law requires a manufacturer to act to update its labeling, a State may impose a similar duty and consequent damages liability for failing to meet that duty. . . . That framework for generic drugs is in harmony with *Wyeth*'s rule for brand-name drugs: Irrespective of whether a drug is approved under an NDA or an ANDA, if the drug was misbranded due to new safety information not reflected in its labeling, then the plaintiff's claims are not preempted. The manufacturer was under a federal duty to revise its federally approved labeling and FDA gave it the ability to seek such changes. Petitioners, by contrast, argue that they enjoy a free pass accorded to virtually no other manufacturer regarding product labeling - in the field of drugs or otherwise. Individuals harmed by inadequately labeled generic drugs would (on petitioners' view) have no remedy against the manufacturer, while individuals who took the same drug with the same labeling in its brand-name form would (by virtue of *Wyeth*) have such a remedy.

Id.

[228] *Mensing*, 131 S. Ct. at 2575 n.3.

[229] The federal preemption doctrines discussed *supra* required an explicit foreclosure by the actual words of the regulations in order to find preemption; it is difficult to understand the majority's strained interpretation of the statute to find conflict preemption given the lack of explicit preemption.

[230] The Court cited to the FDA's concern that "if generic drug manufacturers, but not the brand-name manufacturer, sent such letters, that would inaccurately imply a

on its own it would, per se, be in violation of FDA regulations and lose its status of approval for marketing. The Court's articulation of the enquiry for impossibility preemption turned on "whether the private party could independently do under federal law what state law requires of it."[231] Because the state tort laws required the manufacturers to change their label in spite of this, the Court found that they were federally preempted by the manufacturers' resultant impossibility to comport with both laws. In sum, FDA regulations require "that the warning labels of a brand-name drug and its generic copy must always be the same—thus, generic drug manufacturers have an ongoing federal duty of 'sameness.'"[232] In closing, Justice Thomas "acknowledge[d] the unfortunate hand that federal drug regulation . . . dealt [the patients] and others similarly situated."[233] The majority further clarified that it did not necessarily consider the holding reasonable; "it is not th[e] Court's task to decide whether the statutory scheme established by Congress is unusual or even bizarre."[234]

The dissent, authored by Justice Sotomayor and joined by Justices Ginsburg, Breyer, and Kagan, persuasively disagreed with the state of the law as the majority read it.[235] In disagreeing with the

therapeutic difference between the brand and generic drugs and thus could be impermissibly 'misleading.'" *Mensing*, 131 S. Ct. at 2576 (quoting *Second Brief for the United States*, at *19).

[231] *Id.* at 2571.

[232] *Id.* at 2574–75 (quoting *Second Brief for the United States*, at *16).

[233] *Id.* at 2582.

[234] *Id.* at 2582 (quoting Cuomo v. Clearing House Ass'n, LLC, 129 S. Ct. 2710 (2009)).

[235] *See id.* at 2582–83 (Sotomayor, J., dissenting) (citing the majority opinion at 2581).

> The Court today invokes the doctrine of impossibility pre-emption to hold that federal law immunizes generic-drug manufacturers from all state-law failure-to-warn claims because they cannot unilaterally change their labels. I cannot agree. We have traditionally held defendants claiming impossibility to a demanding standard: Until today, the mere possibility of impossibility had not been enough to establish pre-emption. . . . The Court strains to reach the opposite conclusion. It invents new principles of pre-emption law out of thin air to justify its dilution of the impossibility standard. It effectively rewrites our decision in Wyeth v. Levine, 555 U.S. 555 (2009), which holds that federal law does not pre-empt failure-to-warn claims against brand-name drug manufacturers. And a plurality of the Court tosses aside our repeated admonition that courts should hesitate to conclude that Congress intended to pre-empt state laws governing health and safety. As a result of today's decision, whether a consumer harmed by inadequate warnings can obtain relief turns solely on the happenstance

holding, the Justices asserted a more outcome-based interpretation of preemption—advancing that Congress could never have intended the results likely to come about through the majority's holding.[236] The most offensive aspect of the majority holding was its antithetical impact on "the core principle of the Hatch-Waxman Amendments that generic and brand-name drugs are the 'same' in nearly all respects."[237]

There are an abundance of potential criticisms pertinent to the application of preemption in *Mensing*. It is not challenging for even passive observers to predict that the outcome will fail to adequately and equally protect injured patients, will partially subvert the Congressional intent of FDA regulations, will impermissibly relax the safety standards of manufacturers of inherently dangerous products, and will exponentially increase the responsibilities of an overburdened federal agency. Extensive analysis of the Court's missteps is rendered futile in light of the denial of a rehearing; the legislature must intervene to avert imminent inequitable results.[238]

> of whether her pharmacist filled her prescription with a brand-name or generic drug. The Court gets one thing right: This outcome "makes little sense."

Id.

[236] *Mensing*, 131 S. Ct. at 2591.

[237] *Id.* at 2593. The Justices perceived that obliterating the perception of sameness through dissimilar

> liability rules threaten[s] to reduce consumer demand for generics, at least among consumers who can afford brand-name drugs. They may pose "an ethical dilemma" for prescribing physicians. . . . And they may well cause the States to rethink their longstanding efforts to promote generic use through generic substitution laws. . . . These consequences are directly at odds with the Hatch-Waxman Amendments' goal of increasing consumption of generic drugs.

Id. (citations omitted).

[238] Cases in the wake of *Mensing* have involved legally creative approaches to obtain patient relief, but success in such approaches is elusive. *See, e.g.*, In re Fosamax (Alendronate Sodium) Prod. Liab. Litig. (No. II), No. 08–008, 2011 WL 5903623, at *6 (D.N.J. Nov. 21, 2011) (In a multidistrict litigation proceeding, the appointed court found preemption-by-impossibility for generic manufacturers in claims including breach of express warranty, fraud, misrepresentation, failure to conform to representation, negligent misrepresentation, and violation of consumer protection statutes. Rather than discussing each element, the judge referred to the nature of each claim and held that they were functionally preempted for the same reason as a failure-to-warn claim would be. The court further held that a claim for breach of implied warranty was preempted because "duty of sameness" between brand name and generic manufacturers transfers to design by way of the ANDA bioequivalence requirement.); Metz v. Wyeth LLC, 830 F.Supp.2d 1291 (M.D. Fla. 2011) (declining to reconsider the state's refusal to find liability for brand-name manufacturers where a patient was injured by the generic on the theory that the

VI. PROPOSED SOLUTION

The costs of healthcare are troubling for the nation as a whole and for individual patients, yet, the pursuit of cost-savings must achieve a balance with the protection of public health. Policies aimed at decreasing expenses that pertain to prescription drug use by expanding generic drug utilization have been vastly successful in that sector—continuing to suppress expenditures is critical to fiscal sustainability. Although elimination of tort liability would directly reduce the operating costs of generic drug manufacturers, the temptation must come second to the FDA's central mission of protecting the public health and responsibly fostering innovation. Offices within the FDA itself have admitted that they continuously fall short with respect to independent monitoring and regulation of the prescription drug market,[239]—as the sole overseer of ANDA-approved drug labels, the FDA's overwhelmed state is only likely to continue based on the growth-oriented forecasts of generic drug use and approval. Investigations spanning decades reveal egregious failures that unquestionably overlooked direct harm to patients. Ominously, these failures took place in a time when generic manufacturers were still motivated to some extent by the potential costs of state tort claims, given the explicit preemption of that liability the FDA's competency in oversight is of the utmost importance.

Since the genesis of legal liability in healthcare, tort law has played a crucial role in maintaining safe practices amongst participants in the market. Despite the vast expansion of federal regulation, tort law continues to be recognized as protecting the health and welfare of patients. As recently as 2009, the U.S. Supreme Court has articulated the distinctive benefits of product liability laws in exposing unknown drug hazards, inducing prompt and thorough information-sharing by manufacturers, and compensating victims for their injuries.[240]

Given the interdependent nature of federal and state liability laws in the context of healthcare, federal preemption of tort law has extensive potential to impact injured persons because the FDA does not provide remedy for private injuries. Ultimately, the Court's unambiguous interpretation of the federal regulations in *Mensing* finding preemption for generic manufacturers cannot be overcome

brand-name owed a duty to the patient to update its own label so that the generic manufacturer could do the same).

[239] *See supra* Part IV.A.

[240] *See supra* note 198 and accompanying text.

by subsequent interpretations, no matter how reasonable the argument. Instead, the extensive array of factors that the dissenting justices and the various amicus curiae asserted against finding preemption must now be used to support adaptation of federal regulation in a way that will render preemption of state tort liability for generic drug manufacturers a nullity.

To achieve the dual objectives of affordability and availability of generics on one hand, and their safety on the other, the FDA must find an acceptable middle ground. An example of such compromise by the FDA between the competing priorities of generic drug policies is evident in the expansion of charging user fees to generic manufacturers to help fund FDA oversight. The increased cost to generic manufacturers will be passed on to the consumer, but the increased funding will aid the FDA in oversight of safety; a similar compromise would serve the FDA well with respect to safety and cost and label liability.

This Comment recommends adaptation of the federal regulations pertaining to supplementation of approved drugs in a manner mirroring the post-approval reporting requirements for ANDA-approved drugs. The extensive mandates of 21 C.F.R. § 314.80 lay out the recording and reporting burdens of NDA holders with respect to post-approval adverse events. The equivalent regulation for ANDA holders is 21 C.F.R. § 314.98. Rather than laying out independent requirements, this regulation indiscriminately adopts the directives of § 314.80, requiring the same adverse event record-keeping and reporting as that of brand-name drug manufacturers. This approach is evidence of recognition that manufacturers of generic drugs are in at least an equivalent position to that of brand-name drug manufacturers to collect post-market safety information and report it. Given generics' dominant share of a market following entry, it is more likely that they are in a superior position to collect and report date than their brand-name competitor. Generics account for the vast majority of prescription drug consumption and approximately a third of marketed generics have no brand-name counterpart on the market at all;[241] naturally, absence of public usage eliminates reporting requirements entirely, leaving all data collection to the generic manufacturer.

The CBE method embodied in 21 C.F.R. § 314.70(c)(6)(iii) is derivative of the FDA's prioritization of public safety. Endowing

[241] *See supra* note 71.

independent power to brand-name drug manufacturers to modify their labels in a manner that will sufficiently notify consumers of moderate changes to label warnings is a vehicle of efficiency that errs on the side of disclosure and relinquishes agency control. The language used throughout the regulation to describe warnings that should be updated is rather similar to standards promulgated by most state tort failure-to-warn statutes; both contemplate adequate and fair notice to consumers of safe use and the risks they run in utilizing the enclosed product. In 21 C.F.R. § 314.97, the language directs ANDA holders to § 314.70 for matters necessitating post-market label supplementation. The operation of § 314.97 for generic label changes is, at first glance, equivalent to the adoption of brand-name standards in adverse event reporting for generic drugs. The effects are not interpreted the same though; 21 C.F.R. §314.150 creates a duty of "sameness" with regard to the label of a generic drug and the reference listed drug—this duty trumps the generic manufacturer's ability to make unilateral label changes under § 314.70(c)(6)(iii).[242] In order to influence § 314.97 in a manner that will allow a drug approved pursuant to an ANDA, § 314.150 should be reformed.

Rather than a per se rule that a generic drug must perpetually duplicate the reference listed drug upon which it initially relied for approval, a rule more mutually applicable should be promulgated. Following a pre-determined period, both drugs should be obligated to mimic the label of the other so long as divergent changes do not come to light. The trigger for generic manufacturer independence should be the greater of either a specific lapse of time or a quantified level of market share following its launch. These measures should determine the position a generic manufacturer would need to reach to be capable of collecting sufficient event reports. If the generic manufacturer never reaches the trigger point that has been established, it should continue to be guided by § 314.150. While the concern has been raised that varying labels will decrease the perception of "sameness," this issue is not implicated by the proposed solution. The current regulation allows for a time gap between a brand-name manufacturer's label change and a generic's[243]—allowing a reversal in this order would have no functional impact on consumer perception or use.

The fundamental underlying rationale for the labeling requirement of § 314.150 in its current form is the approval process

[242] *See supra* note 230 and accompanying text.
[243] *See supra* note 230 and accompanying text.

of generic drugs, not the subsequent market use of those drugs.[244] Eventually the generic drug's initial reliance on the reference list drug's safety and efficacy is devoid of utility beyond the cost savings it provided for approval by eradicating the need for clinical trials. Although extensive, costly, and time-consuming, clinical trials conducted for the purposes of a NDA have limited value in terms of long-term safety and realistic patient populations. A novel drug, by definition, is new to the market, thus long-term studies do not exist in the absence of long-term use. Patient populations in new drug studies are limited by strict study parameters, therefore patient-types that will be treated in the real world may not have been significantly represented in the trials, furthermore serious but rarer adverse events often go undiscovered initially. Based upon these weaknesses and the costs of extending or initiating formal studies beyond what is required for approval, long-term safety data is determined extensively through tracking and analysis of the post-market reports compiled by brand and generic manufacturers alike. Upon potential discovery of a previously unknown adverse drug effect, statistical analysis or studies may be required to discern causation.[245] As a tenet of the compromise suggested between maintaining safety and reducing costs, it may be reasonable to require that these studies be conducted by the generic company if they are a market leader, this can be a determination made by the FDA on a case-by-case basis founded on predetermined factors such as market share and so on.

In the absence of reforming FDA regulation of generic drug label practices, the goals of Congress are at risk of subversion. One of the FDA's central purposes is to ensure safety of the drugs it oversees; because Congress created the FDA, this should be considered an aim of Congress as well. Consequently, the focus on safety must coexist with the aim of the Hatch-Waxman Amendments toward driving down the costs of prescription drugs and current legislative emphasis on driving down the cost of healthcare in general. When measuring healthcare costs in a universal sense, it is impossible to ignore the implications of consequences visited upon patients where drug labels fail to adequately warn of certain risks. The cost to patients such as Mensing and Demahy are life-long and will be borne by the public

[244] *See supra* Part II.D.

[245] *See* PAUL SELIGMAN, OFF. OF PHARMACOEPIDEMIOLOGY & STAT. SCIS., FOOD & DRUG ADMIN., ASSESSING DRUG SAFETY DATA: KEY CONCEPTS & ISSUES 21–27 (2003), *available at* http://ocw.jhsph.edu/courses/drugdevelopment/PDFs/Seligman_Safety_Monitoring_Presentation_12_03_03_Rev.pdf.

sector through programs such as disability or Medicare.

Safe use of medicine and cost-effective healthcare go hand-in-hand; *Mensing* fails to strike an adequate balance between cost-savings and safety. Tort liability will undoubtedly drive up the cost of doing business for generic companies, and they are likely to pass that cost along to consumers; however, product liability only requires that warnings be *reasonable*. It is hard to imagine that patients would benefit if generic drug manufacturers were not held to a standard of reasonableness.

Generic drugs can decrease costs for patients only if patients are willing to take them. The present lack of tort liability is likely to create a perception in the collective mind of the consuming public that generic manufacturers do not have the same emphasis on safety that their brand counterparts do. Even in the absence of this concern, consumers may find reason for anxiety in the generic manufacturer's inability to update a label's warning independently where they are compelled to do so. Additionally, if savvy patients lack confidence that they will have avenues for relief when injured by a drug, they are far more likely to demand the costlier brand-name version of that prescription.[246] Alternatively, where patients' prescriptions are substituted at the pharmacy, many are unlikely to be aware of the risks they are taking until they find themselves without remedy in a court of law.

The market of authorized generics further erodes the logic of the comprehensive federal regulation of drug safety; to allow preemption of state tort liability for a brand manufacturer based on packaging would certainly distort congressional intent. Perhaps the single most significant consideration in generic drug cost concerns will be exacerbated by *not* negating *Mensing*. The very states that have been disgorged of private actions for their citizens' tort claims also act as the greatest source of generic prescriptions.[247] The substitution laws of each state are likely to be approached more critically if the states come to consider the dangers of generic consumption as outweighing its benefits. The duty of "sameness" should be limited wherever it is promulgated in the regulations applicable to all post-market activities.

[246] *See supra* note 237 and accompanying text.
[247] *See supra* note 111.

VII. CONCLUSION

While cost savings and reducing barriers in equal access to care are lofty healthcare goals, they should not eviscerate the standard of safety incumbent upon manufacturers of products that are dangerous by their very nature. If a generic drug label does harm by failing to adequately warn physicians or patients about the risks they are taking, it does not atone for this by merely being affordable. There is a level of trust given to the medical community that must be protected in order to forward the goals of healthcare; this trust cannot be maintained if the legislature prevents states from holding producers of medicine accountable for their failures.

In the frenetic and divided political environment of healthcare and the role of government within it, there is major reform underway. The reform maintains and expands long-term appreciation for the merits of generic drug utilization. Cost savings and equality in delivery are especially emphasized goals in the transformation of healthcare, and generics have consistently proven that they deliver in these areas. This Comment does not propose that the ANDA process be disproportionately limited, or that generics should do independent safety or efficacy studies in coming to market. Increasing the cost of bringing a generic drug to market can and should be avoided in addressing the risks created by the holding in *Mensing*; however, the law should not go so far as to inhibit consumer safety. Present legislation should be reformed to allow generic manufacturers to alter their warnings post-approval through the same methods currently available to brand manufacturers. This simple reform would in turn negate the preemption-by-impossibility found in *Mensing* and maintain a critical balance between controlling healthcare costs and preserving safety. Cost savings in the market will not be achieved by incentivizing patients to demand more expensive products, or by reducing the motivation in the market for drug manufacturers to produce and maintain effective warning labels.

Generic drugs account for the vast majority of prescriptions consumed. If they lead to greater harm than a brand-manufacturer's product does, it is very likely to drive up the cost of care in this country, and this result is the exact opposite of the Congressional goals behind the Hatch-Waxman Amendments. By affording generic drug manufacturers the ability to increase safety warnings through the same mechanisms as their brand-name counterparts, the legislature will prevent the harmful results that will inevitably follow the holding in *Mensing*.