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Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
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Rockville, MD 02852

**COMMENTS ON PROPOSED RULE:
“SUPPLEMENTAL APPLICATIONS PROPOSING LABELING CHANGES FOR
APPROVED DRUGS AND BIOLOGICAL PRODUCTS”
RIN 0910-AG94**

Public Citizen, a consumer organization with members and supporters nationwide, submits these comments in strong support of the proposed rule on supplemental applications proposing labeling changes for approved drugs and biological products, published in the Federal Register on November 13, 2013. When finalized, the proposed rule will enable generic drug manufacturers to revise generic drug labeling through the changes-being-effected (CBE-0) procedures.

As discussed below, since enactment of the Hatch-Waxman Amendments in 1984, the prescription-drug market has been transformed, as sales of generic drugs have skyrocketed and such drugs now constitute the vast majority of all prescriptions filled. Yet despite considerable changes in the market, FDA regulation of generic labeling has remained substantially unchanged. Public Citizen therefore strongly supports the agency’s proposal, which will bring post-market regulation of generic drugs in line with the realities of the pharmaceutical market and help ensure that drug labeling provides adequate warnings to patients based on information that comes to light after drugs are approved for marketing.

I. THE PROPOSED RULE WILL IMPROVE THE SAFETY OF PRESCRIPTION DRUGS.

A. Manufacturers of Generic Drugs Produce a Majority of the Prescription Drugs Sold in the United States.

Following passage of the Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585, commonly referred to as the Hatch-Waxman Amendments,

sales of generic drugs have grown dramatically, fundamentally reshaping the pharmaceutical market. The increased availability of generic drugs has made many prescription drugs more affordable for patients.¹ In 1983, only 35 percent of top-selling drugs with expired patents had generic equivalents; by 1998, nearly all did.² And when generics compete, they typically capture a significant part of market share and profit.³ As of 2010, 90 percent of prescriptions for drugs with generic versions were filled with generics rather than brand-name drugs⁴—a development spurred by state laws authorizing pharmacists to substitute generic drugs when filling prescriptions.⁵ Some states have gone further and now mandate generic substitution where available.⁶ From 2009 through 2012, generic prescriptions' share of the prescription drug market increased by another 10 percent, to reach 84 percent of all U.S. prescriptions.⁷ In 2010, generics captured more than 80 percent of the market within six months of expiration of a brand-name's patent (as compared to 55 percent in 2006).⁸ Generic market leader Teva boasts that “[o]ne in every six prescriptions dispensed in the U.S. is a Teva product.”⁹

Generic manufacturers' market growth has been accompanied by an expansion in their profit margins and research capabilities. Obtaining FDA approval for a generic drug requires a significant investment of scientific expertise and research funding.¹⁰ Generic manufacturers accordingly spend millions of dollars annually on research and development.¹¹

In some cases, brand-name and generic research and development overlap. For example, the top-selling generic manufacturer in the U.S., Teva, “has a significant and growing branded pharmaceutical portfolio.”¹² And two of the top five generic manufacturers are divisions of major brand-name manufacturers with well-known new drug research programs (Sandoz and Greenstone, which are divisions of Novartis Corp. and Pfizer Inc., respectively).¹³

¹ Generic Pharm. Ass'n, *Generic Drug Savings in the U.S.* (4th ed. 2012) (GPhA 2012 Study).

² Congressional Budget Office, *How Increased Competition From Generic Drugs Has Affected Prices and Return in the Pharmaceutical Industry*, at xii (1998).

³ See Congressional Budget Office, *Research and Development in the Pharmaceutical Industry* 16-17 (2006).

⁴ HHS, *ASPE Issue Brief: Expanding the Use of Generic Drugs* 3-4 (Dec. 2010).

⁵ See Thomas P. Christensen *et al.*, *Drug Product Selection: Legal Issues*, 41 J. Am. Pharm. Ass'n 868 (2001).

⁶ William H. Shrank *et al.*, *State Generic Substitution Laws Can Lower Drug Outlays Under Medicaid*, 29 Health Affairs 1383 (July 2010).

⁷ IMS Institute for Healthcare Informatics, *Declining Medicine Use and Costs: For Better or Worse?* (May 2103); IMS Institute for Healthcare Informatics, *The Use of Medicines in the United States: Review of 2010* at 11, 15, 22 (April 2011) (IMS Report 2011).

⁸ IMS Report 2011, *supra* note 7, at 21.

⁹ Teva North America, *Our Products*, at <http://www.tevapharm-na.com/Our-Products.aspx>.

¹⁰ See David Reiffen & Michael R. Ward, *Generic Drug Industry Dynamics*, 87 Rev. of Econ. & Stats. 37, 38 (2005) (“In the vast majority of cases, the initial ANDA application is found deficient, requiring the applicant to conduct additional tests or submit additional material.”).

¹¹ See, e.g., Teva Pharm. Indus. Ltd, *Annual Report 2012*, at 3 (2013), available at <http://ir.tevapharm.com/phoenix.zhtml?c=73925&p=irol-reportsAnnual>; see also Teva Pharm. Indus. Ltd, *Annual Report 2009*, at 48 (2010) (noting that in 2009 Teva Pharmaceuticals spent approximately 63 percent of a total \$802 million in R&D expenses on generic R&D).

¹² See Teva North America, *Our Products*, <http://www.tevapharm-na.com/Our-Products.aspx>.

¹³ See Alaric Dearment, *Countdown to 2011: A Big Year for Generics*, Drug Store News, Nov. 14 2010, available at <http://www.drugstorenews.com/article/countdown-2011-big-year-generics>.

Successful competition from generics has led some brand-name manufacturers to cease production of out-of-patent drugs. A group of health policy experts and professors of pharmaceutical regulation found, based on analysis of FDA data, that “out of 4,653 approved drugs with distinct ingredients, delivery routes, and strengths, more than half—2,438—are available in generic form. Of those, 1,062 are available *solely* in generic form; the only available versions of the drug received ANDA [abbreviated new drug application] approval.”¹⁴ A 2010 study by the Generic Pharmaceutical Association reported that, in 2009, 32 percent of 4,318 unique drug molecules were sold *solely* as generics.¹⁵ A 2012 study by the Generic Pharmaceutical Association notes that, for 45 percent of generics sold, no branded product is currently on the market.¹⁶ The FDA recently estimated the number of ANDAs with unique active ingredients for which the reference listed drug (RLD) is no longer marketed as approximately 420.¹⁷

B. Continuous Post-Approval Monitoring Is Essential to Drug Safety and Is a Shared Responsibility of The FDA and All Manufacturers.

1. As the Supreme Court recognized in *Wyeth v. Levine*, “[t]he 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.”¹⁸ It has therefore been “a central premise of federal drug regulation that the manufacturer bears responsibility for the content of its label at all times . . . [and] ensuring that its warnings remain adequate as long as the drug is on the market.”¹⁹ The need for manufacturers to play a significant role is heightened by funding and staff shortages at the FDA that have prompted the Government Accountability Office (GAO) repeatedly to express concern about post-approval drug safety monitoring.²⁰

To ensure the post-approval safety of their drugs, all manufacturers—brand-name and generic—must comply with an extensive set of regulations. Of particular relevance, manufacturers “shall promptly review all adverse drug experience information obtained or otherwise received by the applicant from any source, foreign or domestic, including information derived from commercial marketing experience, post-marketing clinical investigations,

¹⁴ Brief for Marc T. Law et al. as Amici Curiae Supporting Resp’ts, *Pliva v. Mensing*, 131 S. Ct. 2567 (2011) (Nos. 09–993, 09–1039, 09–1501) at 18 (Brief of Pharm. Reg. Experts).

¹⁵ Generic Pharm. Ass’n, *Savings Achieved Through the Use of Generic Pharmaceuticals 2000-2009*, at 7 (2010).

¹⁶ GPhA 2012 Study, *supra* note 1 at 8.

¹⁷ FDA, *Supplemental Applications Proposing Labeling Changes for Approved Drugs and Biological Products, Preliminary Regulatory Impact Analysis* at 9 (2013) (FDA Regulatory Impact Analysis).

¹⁸ 555 U.S. 555, 578-79 (2009) (footnote omitted).

¹⁹ *Id.* at 570-71.

²⁰ See, e.g., GAO, *High-Risk Series: An Update* 116-17 (Feb. 2011) (“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.”); GAO, *Drug Safety: FDA Has Begun Efforts to Enhance Postmarket Safety, But Additional Actions Are Needed* (Nov. 2009); GAO, *Drug Safety: Improvement Needed in FDA’s Postmarket Decisionmaking and Oversight Processes* (Mar. 2006); see also David A. Kessler & David C. Vladeck, *A Critical Examination of the FDA’s Efforts to Preempt Failure-to-Warn Claims*, 96 Geo. L.J. 461, 485 (2008) (noting that “[r]esource constraints have been especially acute with the agency’s post-marketing surveillance efforts” and that two-thirds of FDA doctors and scientists “worry that the FDA is not adequately monitoring the safety of drugs once they are on the market”).

postmarketing epidemiological/surveillance studies, reports in the scientific literature, and unpublished scientific papers.”²¹ Any report of a “serious and unexpected” drug experience, whether foreign or domestic, must be reported by the manufacturer to the FDA within 15 days and must be promptly investigated by the manufacturer.²² Other adverse event reports must be submitted quarterly for three years after the application is approved and annually thereafter.²³ These periodic reports must include “a history of actions taken [by the manufacturer] since the last report because of adverse drug experiences (for example, labeling changes or studies initiated).”²⁴ Generic manufacturers, like their brand-name counterparts, must therefore participate actively in ongoing pharmacovigilance to comply with FDA regulations.

To ensure that labeling is kept up to date as information accumulates, FDA regulations require that the labeling of *both brand-name and generic drugs* “must be revised to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association with a drug; a causal relationship need not have been definitely established.”²⁵

Brand-name manufacturers, who market drugs approved through the new drug application (NDA) process, may seek review and approval of revised labeling by filing a supplemental application.²⁶ A supplemental application must satisfy all regulatory requirements that apply to original applications.²⁷ Although some label changes require prior FDA approval—obtained through a prior approval supplement (PAS)²⁸—other changes are brought to FDA’s attention “at the time the applicant makes [the] change” through a CBE-0 supplement.²⁹ CBE-0 supplements are authorized for, among other things, “[c]hanges in the labeling to reflect newly acquired information . . . [t]o add or strengthen a contraindication, warning, precaution, or adverse reaction for which the evidence of a causal association satisfies the standard for inclusion in the labeling under § 201.57(c) of this chapter.”³⁰

By its terms, the CBE-0 regulation would seem to apply already to both generic and brand-name manufacturers.³¹ However, the U. S. Supreme Court, deferring to the FDA’s interpretation of the existing regulation, has held that the CBE-0 process is not available to generic manufacturers.³² Instead, ANDA holders can make safety updates only after approval of a CBE-0 supplement submitted by the NDA holder for the RLD or when ordered to by the FDA.³³ This

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

²² *Id.* § 314.80(c)(1)(i-ii).

²³ *Id.* § 314.80(c)(2)(i).

²⁴ *Id.* § 314.80(c)(2)(ii).

²⁵ *Id.* § 201.57(c)(6)(i) (implementing 21 U.S.C. § 352(f)(2), which provides that a drug lacking “adequate warnings” is misbranded).

²⁶ *Id.* § 314.70.

²⁷ *See id.* § 314.3(b).

²⁸ *Id.* § 314.70(b).

²⁹ *Id.* § 314.70(c).

³⁰ *Id.* § 314.70(c)(6)(iii)(A).

³¹ *See also id.* § 314.97 (requiring ANDA holders to comply with “requirements [applicable to NDA holders] regarding the submission of supplemental applications”).

³² *PLIVA, Inc. v. Mensing*, 131 S. Ct. 2567, 2575 (2011).

³³ FDA, Guidance for Industry, *Revising ANDA Labeling Following Revision of the RLD Labeling* 5 (May 2000), at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072891.pdf> (FDA Guidance).

restriction follows from the general rule that the labeling of the generic product must generally be “the same as the labeling of the reference listed drug [RLD].”³⁴ At the same time, the regulations allow variations between brand-name and generic labeling for certain types of information,³⁵ and during the period in which a brand-name CBE-0 supplement is pending approval.

2. The importance of post-approval monitoring for drug safety is well-recognized. As an article in the Journal of the American Medical Association explained:

Even though the evaluation of new drugs and devices is technically rigorous, the current approach of basing drug approval decisions on clinical trials of efficacy that include relatively small numbers of patients virtually guarantees that the full risks and complete safety profile of these drugs will not be identified at the time of approval. Rather, the full safety profile and effectiveness only manifest as each drug is used in the wider population of patients who are less carefully selected than participants in clinical trials.³⁶

The limitations in pre-approval testing are especially salient when a drug’s significant adverse effects are relatively rare or have long latency periods—forms of risk that the FDA approval process is not designed to uncover.³⁷ Examples of drugs whose substantial risks were only discovered post-approval abound in the medical literature.³⁸ In particular, off-label uses, some of which become popular after a generic option is on the market, may lead to unforeseen side effects.³⁹ As a 2013 article authored jointly by three FDA staff members and two academics reported: “The most critical safety-related label changes, boxed warnings and contraindications, occurred a median 10 and 13 years after drug approval (and the range spanned from 2 to 63 years after approval), underscoring the importance of persistent and vigilant postmarket drug safety surveillance.”⁴⁰ This conclusion is consistent with the finding that “only half of newly discovered serious [adverse drug reactions] are detected and documented in the *Physician’s Desk Reference* within 7 years after drug approval.”⁴¹

³⁴ 21 C.F.R. § 314.94(a)(8)(iii); *see also id.* § 314.105(c).

³⁵ *See id.* § 314.94(a)(8)(iv), discussed *infra* at page 13.

³⁶ Catherine D. DeAngelis & Phil B. Fontanarosa, *Prescription Drugs, Products Liability, and Preemption of Tort Litigation*, 300 J. Am. Med. Ass’n 1939, 1939 (2008).

³⁷ Kessler & Vladeck, *supra* note 20, at 483.

³⁸ *See* Brief of the Am. Med. Ass’n, et al. as Amici Curiae Supporting Resp’ts, *PLIVA, Inc. v. Mensing*, 131 S. Ct. 2567 (2011) (Nos. 09–993, 09–1039, 09–1501), at 12–17 (discussing as examples fenfluramine, propoxyphene, ibuprofen, terbutaline sulfate, and metoclopramide); Brief of Pharm. Reg. Experts 29–30 (discussing Neurontin, metoclopramide, and Darvon).

³⁹ *See* Brief of Pharm. Reg. Experts 30–31 (discussing example of trazodone).

Moreover, some generic drugs may be associated with adverse events that do not occur with the brand-name drug. *See* Brief of Pharm. Reg. Experts 30–31 (discussing Budeprion XL as an example of a generic drug with side effects not associated with Wellbutrin XL, its brand-name counterpart). Under current regulations, the FDA has sole responsibility for updating generic labeling to reflect such hazards, as the generic manufacturer may not revise labeling on its own to reflect newly discovered hazards.

⁴⁰ Jean Lester, et al., *Evaluation of FDA safety-related drug label changes in 2010*, 22 *Pharmacoepidemiology and Drug Safety* 302, 304 (2013).

⁴¹ Karen E. Lasser, et al., *Timing of New Black Box Warnings and Withdrawals for Prescription Medications*, 287 J. Am. Med. Ass’n 2215, 2218 (2002).

Recently, Public Citizen undertook to compile a list of drugs for which black-box warnings—reserved for the most serious contraindications and warnings—were added after a generic equivalent entered the market. Restricting our research to a five-year period, we identified 53 drugs for which a black-box warning calling attention to serious or life-threatening risks was added after generic market entry—and the list is likely incomplete. The data show that new safety issues commonly arise after generics have entered the market, and they underscore the public health imperative of maintaining an incentive for generic manufacturer surveillance of safety concerns.⁴²

The following examples illustrate the severe risks set forth in black-box warnings added 10 or more years after approval of a drug and after a generic equivalent entered the market:

- Promethazine hydrochloride, originally marketed under the brand name Phenergan, was approved by the FDA in tablet form in 1951, in injectable form in 1956, and in suppository form in 1960.⁴³ It is approved for several indications, including for treatment of motion sickness, nausea, and some allergy symptoms. In 2000, the warning was strengthened to recommend against use in children younger than two years old, and in 2004, the FDA required a boxed warning instructing against the use of the drug in pediatric patients under two years old.⁴⁴ The boxed warning was added after adverse event reports of respiratory depression, including fatalities, in children under age two.⁴⁵ Brand-name Phenergan was later discontinued but generic versions of promethazine are still available.⁴⁶ In 2009, the FDA required an additional boxed warning for injectable promethazine hydrochloride due to the risk of gangrene if the drug enters an artery.⁴⁷
- Metoclopramide hydrochloride, sold under the brand name Reglan and other names, was approved to treat gastrointestinal problems in three dosage forms: an injectable formulation approved in 1979, a tablet approved in 1980, and an oral solution approved in 1983.⁴⁸ The drug received its first black-box warning in 2009, 30 years after its first approval, after doctors discovered that its use could cause tardive dyskinesia in certain patients.⁴⁹ Tardive dyskinesia is a serious, often irreversible movement disorder that causes involuntary, repetitive movements of the extremities, as well as lip smacking, grimacing, tongue protrusion, and other uncontrollable facial movements.⁵⁰ When the

⁴² The Public Citizen report is available at <http://www.citizen.org/documents/2138.pdf>.

⁴³ FDA, Drugs@FDA, Phenergan, available at <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>.

⁴⁴ FDA, Drugs@FDA, Promethazine Hydrochloride, label as approved on Nov. 8, 2004, at http://www.accessdata.fda.gov/drugsatfda_docs/label/2004/07935s0301bl.pdf; Letter to the Editor, *Boxed Warning Added to Promethazine Labeling for Pediatric Use*, *New Eng. J. Med.* 2653 (2005), at <http://www.nejm.org/doi/full/10.1056/NEJM200506233522522> (letter from FDA staff).

⁴⁵ Letter to the Editor, *supra* note 44.

⁴⁶ FDA, *Information for Healthcare Professionals: Intravenous Promethazine and Severe Tissue Injury, Including Gangrene*, (Sept. 16, 2009), at <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHealthcareProfessionals/ucm182169.htm>.

⁴⁷ *Ibid.*

⁴⁸ FDA, Drugs@FDA, Reglan, available at <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>.

⁴⁹ FDA, *Metoclopramide-containing drugs* (Feb. 26, 2009), at <http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm106942.htm>.

⁵⁰ *Ibid.*

FDA announced the warning in 2009, the agency estimated that more than 2 million Americans were taking products that contained metoclopramide hydrochloride.⁵¹

- Propoxyphene hydrochloride, sold under the brand name Darvon or Darvocet, was approved by the FDA in 1957. In 2007 alone, more than 21 million prescriptions were filled for the generic combination of propoxyphene and acetaminophen, making it one of the most widely distributed generic drugs in the United States.⁵² In 2009, the FDA announced that additional labeling was needed to reduce the risk of overdose in people who use propoxyphene and other pain medications. The revisions included strengthening the boxed warning on products containing propoxyphene to emphasize the risk of overdose.⁵³ At the FDA's request, manufacturers removed Darvon and Darvocet and all generic versions from the market in 2010—53 years after it came on the market—citing evidence that the drug can cause “serious toxicity to the heart.”⁵⁴
- Pemoline was approved by the FDA in 1975 under the brand name Cylert to treat attention deficit hyperactivity disorder.⁵⁵ A black-box warning was added 22 years later, in 1997, after the FDA became aware of at least 10 cases of liver failure associated with use of the drug.⁵⁶ By December 1998, a total of 15 cases had been identified, a much higher rate than expected in the general population.⁵⁷ Of these, 12 resulted in death or required a liver transplant.⁵⁸ In 1999-2001, the FDA approved several generic versions of the drug.⁵⁹ The brand-name manufacturer removed the drug from the market in 2005, and, at the agency's request, the generic companies agreed to stop marketing the product.⁶⁰
- Fluoxetine hydrochloride, approved by the FDA as Prozac in 1987,⁶¹ is prescribed to treat depression and other serious psychological disorders.⁶² In 2004, citing heightened risk of suicide in children and adolescents, the FDA directed the manufacturers of all selective

⁵¹ FDA, *FDA requires boxed warning and risk mitigation strategy for Metoclopramide-containing drugs* (Feb. 26, 2009), at <http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm149533.htm>.

⁵² Sidney M. Wolfe, M.D., *Testimony on Propoxyphene (Darvon) Before FDA's Anesthetic, Analgesic and Rheumatologic Drugs and Drug Safety and Risk Management Advisory Committees* (Jan. 30, 2009), at www.citizen.org/Page.aspx?pid=537.

⁵³ FDA, *FDA Takes Action on Darvon and Other Pain Medications* (July 14, 2009), at <http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm171714.htm>.

⁵⁴ FDA, *Propoxyphene: Withdrawal – Risk of Cardiac Toxicity* (Nov. 19, 2010), at <http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm234389.htm>.

⁵⁵ FDA, Drugs@FDA, Cylert, available at <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>.

⁵⁶ FDA, Drugs@FDA, Cylert Label and Approval History (Dec. 12, 1997), at http://www.accessdata.fda.gov/drugsatfda_docs/nda/97/016832a_s015.pdf.

⁵⁷ FDA, Drugs@FDA, Cylert Label and Approval History, label as revised Dec. 2002, at http://www.accessdata.fda.gov/drugsatfda_docs/label/2003/016832s022_017703s0181bl.pdf.

⁵⁸ *Ibid.*

⁵⁹ FDA, Drugs@FDA, Pemoline, available at <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>.

⁶⁰ FDA, *Information for Healthcare Professionals: Pemoline Tablets and Chewable Tablets (marketed as Cylert)*, at <http://www.fda.gov/drugs/drugsafety/postmarketdrugssafetyinformationforpatientsandproviders/ucm126461.htm>.

⁶¹ The same new drug application submitted for Prozac and approved in 1987 (NDA #018936) also supports marketing of the drug under the brand name Sarafem. FDA, Drugs@FDA, Sarafem, available at <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>.

⁶² FDA, Drugs@FDA, Fluoxetine Hydrochloride 1, at http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/018936s097s098,021235s019s0201bl.pdf.

serotonin reuptake inhibitor (SSRI) anti-depressants, including fluoxetine, to revise the labeling to include a black-box warning.⁶³ That warning was later extended to adults under 25 who were prescribed an SSRI.⁶⁴ Fluoxetine remains on the market today in both brand-name and generic form.⁶⁵

- Haloperidol is an antipsychotic drug approved by the FDA in 1971 under the brand name Haldol.⁶⁶ In 2007, the FDA announced that the sponsor of the drug had updated the warning label due to reports of sudden death and heart-related side-effects.⁶⁷ In 2008, the FDA required manufacturers of haloperidol and many other antipsychotic drugs to add black-box warnings following the release of several studies suggesting that the use of these types of drugs to treat elderly patients with dementia increased the risk of death among these patients.⁶⁸

The Public Citizen report also provided information about drugs currently sold exclusively in generic form, with no current brand-name version on the market. Based on information in the FDA's *Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations*,⁶⁹ we identified 434 approved drugs for which *no* brand-name product remains on the market.⁷⁰ As noted earlier, the FDA's estimate is approximately 420 drugs with unique active ingredients,⁷¹ and the Generic Pharmaceutical Association has put the number even higher, stating that for 45 percent of generics, no branded product is currently on the market.⁷² In that situation, the limitation on generic manufacturers' ability to update labeling to provide the most current warning information takes on added significance, particularly for drugs known to have serious risks, because the brand-name manufacturer is not conceivably going to use resources to monitor the safety of a drug that it is no longer selling, much less to update labeling for the drug. The market withdrawals of Accutane and Serzone illustrate the point.

Accutane, the brand name of the drug isotretinoin, is used to treat a severe form of acne and first received FDA approval in 1982.⁷³ Accutane was linked to several severe side effects, including birth defects when taken by pregnant women, damage to the liver and other internal

⁶³ FDA, *Suicidality in children and adolescents being treated with antidepressant medications* (Oct. 15, 2004), at <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHealthcareProfessionals/PublicHealthAdvisories/ucm161679.htm>.

⁶⁴ FDA, *Antidepressant use in children, adolescents, and adults* (May 2, 2007), at <http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm096273.htm>.

⁶⁵ FDA, Drugs@FDA, Fluoxetine and Fluoxetine Hydrochloride, both available at <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>.

⁶⁶ FDA, Drugs@FDA, Haldol, available at <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>.

⁶⁷ FDA, *Information for HealthCare Professionals: Haloperidol (marketed as Haldol, Haldol Decanoate and Haldol Lactate)* (Sept. 2007), at <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHealthcareProfessionals/ucm085203.htm>.

⁶⁸ FDA, *Information for HealthCare Professionals: Conventional Antipsychotics* (June 16, 2008), at <http://www.fda.gov/drugs/drugsafety/postmarketdrugssafetyinformationforpatientsandproviders/ucm124830.htm>.

⁶⁹ FDA, *Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations* (2013), at <http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm>.

⁷⁰ See Public Citizen Report, *supra* note 42, at 11-23.

⁷¹ See *supra* p. 3 & note 17.

⁷² See *supra* p. 3 & note 16.

⁷³ FDA, Drugs@FDA, Accutane, at <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>.

organs, and depression.⁷⁴ In 2009, after nearly 30 years on the market, the brand-name manufacturer discontinued manufacturing and distributing Accutane, citing the cost of personal-injury lawsuits and the effect of generics on its market share.⁷⁵ Generic versions of isotretinoin remain available.⁷⁶

Serzone, the brand name of the antidepressant nefazodone hydrochloride, was approved in 1994 and removed from the market by the brand-name manufacturer in 2004.⁷⁷ Although the drug, which is associated with liver failure,⁷⁸ had been withdrawn from the market in Canada for safety reasons,⁷⁹ the company stopped selling it in the United States, purportedly because of economic considerations.⁸⁰ Generic nefazodone hydrochloride remains on the market.⁸¹

In sum, our research confirms the findings of the 2010 FDA study, referred to in the proposed rule,⁸² that “critical safety-related label changes” may occur many years *after* approval, *after* entry of the generic onto the market, and *after* exit of the brand name. These findings highlight the crucial importance of allowing generic manufacturers to update product labeling.

C. Allowing Generic Manufacturers to Take Responsibility for Ensuring the Post-Approval Adequacy of Product Labeling Will Make Products Safer.

The FDA’s position that the CBE-0 procedure is currently unavailable to ANDA holders, and the Supreme Court’s 2011 decision in *PLIVA, Inc. v. Mensing*, which deferred to the FDA’s position on that question in holding that state common-law claims for injuries caused by generic drugs are preempted,⁸³ threaten the safety of prescription drugs and, accordingly, pose unnecessary risks to patients.

First, the rise of generics has weakened incentives for brand-name manufacturers to remain actively engaged in post-market surveillance, as the law requires, after losing patent protection.

As explained above, generics compete effectively with out-of-patent brand-name drugs, making prescription drugs more affordable and quickly acquiring a majority market share. The brand-name manufacturer’s financial interest in devoting resources to post-market vigilance

⁷⁴ Roche Laboratories, Inc., *Medication Guide: Accutane* 14-15 (Jan. 2010), at http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/018662s061MedGuide.pdf.

⁷⁵ Roche Pharmaceuticals, *Roche Discontinues and Plans to Delist Accutane in the U.S.* (June 29, 2009), at <http://www.rocheusa.com/portal/synergy/static/file/synergy/alfproxy/download/1414-cd2ddc12b4d211deadd62f6357bc6b3c/>.

⁷⁶ FDA, Drugs@FDA, Isotretinoin, available at <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>.

⁷⁷ 69 Fed. Reg. 62447, 62447 (Oct. 26, 2004), at <http://www.fda.gov/OHRMS/DOCKETS/98fr/04-23857.pdf>.

⁷⁸ Public Citizen, *Petition to ban antidepressant nefazadone (Serzone)* (Mar. 6, 2003), at <http://www.citizen.org/Page.aspx?pid=3299>.

⁷⁹ Health Canada, *Advisory* (Nov. 10, 2003), at <http://www.antidepressantsfacts.com/2003-11-27-nefazodone-canada-withdrawn.htm>.

⁸⁰ CBS Evening News, *Anti-Depressant Taken Off Market* (Dec. 5, 2007), at <http://cbsn.ws/17nn53l>.

⁸¹ FDA, Drugs@FDA, Nefazodone hydrochloride, available at <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>.

⁸² 78 Fed. Reg. at 67988.

⁸³ 131 S. Ct. 2567, 2576 (2011).

decreases when its market share drops from 100 percent to 20 percent or less, which may occur as quickly as within six months after the generic enters the market.⁸⁴

In addition, under the products liability law of many states, the brand-name company cannot be held liable for harm caused by inadequate labeling where the injured patient took a generic form of the drug.⁸⁵ When 84 percent of all prescriptions are filled by generic versions, this legal reality further diminishes the NDA holder's incentive to be vigilant and to take the time and expense to submit a CBE-0 after approval of an ANDA.

Accordingly, as generic market share increases, the brand-name manufacturer loses incentive to invest resources in post-approval safety monitoring.⁸⁶ And it is not uncommon for a brand-name manufacturer to stop selling an off-patent drug altogether, as discussed above.⁸⁷ In that circumstance, if generic manufacturers are not actively monitoring and proposing safety updates, no manufacturer is doing so at all. Given that the FDA cannot monitor all post-approval data by itself, drug safety is threatened when regulatory and common-law incentives designed to motivate manufacturer diligence weaken with shifting control of market share.

Second, the regulatory system has failed to adjust by enabling generic manufacturers to shoulder responsibility commensurate with their status as major market players. Until the proposed rule is finalized, FDA regulations prevent generic manufacturers from providing physicians and patients with updated safety information in light of newly discovered risks. The generic manufacturers are able only to report concerns to the FDA. Yet those manufacturers frequently control most—and sometimes all—of a drug's market share.⁸⁸ Even more important, because of their market share, they receive adverse event reports, may be best informed regarding risks unique to off-label uses, and already must compile information about risks on a periodic basis under post-approval reporting regulations. Drug safety would benefit if generic manufacturers who already have access to much of the relevant information were able to use CBE-0 procedures to revise labeling.

Until 1985, the FDA generally required prior approval for labeling changes.⁸⁹ The FDA revised this approach at the urging of the Pharmaceutical Manufacturers Association and Parke-Davis, who “petitioned FDA to expand the kinds of changes an applicant can make under an approved application and place in effect before receiving agency approval of the change.”⁹⁰ They argued that the pre-approval requirement was unnecessary, took FDA reviewers away from more important work, and caused costly delays. In response, the agency identified numerous types of changes that could be effected without prior approval, including “[c]hanges that add or strengthen a contraindication, warning, precaution, or statement about an adverse reaction, drug abuse, dependence, or overdose, or any other instruction about dosage and administration that

⁸⁴ See IMS Report, *supra* note 7, at 21.

⁸⁵ *Wyeth, Inc. v. Weeks*, ___ So. 3d ___, 2013 WL 135753, at *1 n.5 (Ala. 2013) (collecting cases).

⁸⁶ See *Wyeth*, 129 S. Ct. at 1200 (“[S]tate-law remedies further consumer protection by motivating manufacturers ... to give adequate warnings.”).

⁸⁷ See *supra* page 8 & notes 69-71.

⁸⁸ See *supra* page 2.

⁸⁹ See 47 Fed. Reg. 46622, 46634 (1982).

⁹⁰ *Id.* at 46634-35.

is intended to improve the safe use of the product.”⁹¹ These changes, the FDA said, “would help concentrate the agency’s limited resources more on applications for marketing, and would also permit pharmaceutical manufacturers to institute certain postmarketing changes sooner.”⁹²

The concerns that motivated the FDA to adopt the CBE-0 option—the need to promptly inform physicians and patients, and the interest in efficiency and resource management—apply equally here. As was true then, the agency lacks the resources to be the primary instigator of post-approval labeling changes and cannot timely pre-approve every safety update to the labeling of every approved drug. And as was true then, safety information often comes to light or is clarified *after* initial approval. What is different now, though, is that generic drugs comprise such a large percentage of all prescriptions filled and such an overwhelming percentage of all prescriptions filled for off-patent products, as discussed above. Therefore, today, to fulfill the goal of providing timely labeling updates to physicians and patients, the CBE-0 process must be available to generic, as well as to brand-name, manufacturers.

The proposed rule changes would not impose an obligation beyond the capacity of generic manufacturers. As the FDA stated in its proposal, ANDA holders, like NDA holders, “have an ongoing obligation to ensure their labeling is accurate and up-to-date,” and their products are misbranded when they fail to fulfill this obligation.⁹³ “[A]ll holders of NDAs, ANDAs, and BLAs are required to develop written procedures for the surveillance, receipt, evaluation, and reporting of postmarketing adverse drug experiences to FDA.”⁹⁴ These same regulations require all application holders to promptly review all adverse drug experience information obtained from any source. They must also comply with other postmarketing report requirements, including submission of an annual report and, if appropriate, proposed revisions to product labeling.⁹⁵ Further, FDA regulations have long required ANDA holders to “comply with the requirements of §§ 314.70 and 314.71 regarding the submission of supplemental applications and other changes to an approved abbreviated application.”⁹⁶ In short, the proposed rule does not impose new obligations, but it bolsters incentives crucial to drug safety.

Third, the holding in *Mensing*—that because current FDA regulations do not allow generic manufacturers to revise drug labeling except in response to a brand-name revision, state common-law duties are preempted—produces “absurd consequences.”⁹⁷

As the FDA stated in the proposed rule, “[t]he *Mensing* decision alters the incentives for generic drug manufacturers to comply with current requirements to conduct robust postmarketing surveillance, evaluation, and reporting, and to ensure that the labeling for their

⁹¹ *Id.* at 46635.

⁹² *Ibid.*

⁹³ 78 Fed. Reg. at 67987.

⁹⁴ *Id.* at 67986 (citing 21 C.F.R. §§ 314.80(b), 314.98(a), 600.80(b)).

⁹⁵ *See* 21 C.F.R. § 314.81.

⁹⁶ *Id.* § 314.97.

⁹⁷ *Mensing*, 131 S. Ct. at 2592 (Sotomayor, J, dissenting). *See id.* at 2581 (majority opinion) (“We acknowledge the unfortunate hand that federal drug regulation has dealt *Mensing* ... and others similarly situated. But it is not this Court’s task to decide whether the statutory scheme established by Congress is unusual or even bizarre.”) (citation and internal quotation marks omitted).

drugs is accurate and up-to-date.”⁹⁸ In addition, it denies compensation to consumers injured by drugs with inadequate warnings on the arbitrary basis of whether their prescriptions were filled with a brand-name or generic. In this way, the holding—and the regulatory scheme on which it is based—creates a crucial distinction between brand-name and generic drugs: “Consumers of brand-name drugs can sue manufacturers for inadequate warnings; consumers of generic drugs cannot.”⁹⁹ The FDA expressed similar concerns in its *Mensing* amicus brief, explaining to the Court that if generic manufacturers were to prevail they would “enjoy a free pass accorded to virtually no other manufacturer regarding product labeling—in the field of drugs or otherwise.”¹⁰⁰

The virtues of state common law as an adjunct to FDA drug safety regulations are well-established. As Justice Stevens explained in *Wyeth*:

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 [Food, Drug, and Cosmetic Act’s] premise that manufacturers, not the FDA, bear primary responsibility for their drug labeling at all times.¹⁰¹

State-law remedies thus “further consumer protection by motivating manufacturers to produce safe and effective drugs and to give adequate warnings.”¹⁰² Post-*Mensing*, preemption of common-law claims against generic manufactures strips a vast portion of the market of these safeguards.

Generic manufacturers’ immunity from state common-law suits is contingent on the Supreme Court’s finding that the manufacturers cannot change their products’ labeling under current FDA regulations, even if they learn about new risks. According to the Court, the inability to change labeling renders it impossible for generic manufacturers to comply with both federal and state obligations, giving rise to implied preemption of state law. Amending FDA regulations to permit generic manufactures to make use of CBE-0 procedures in response to new risk information would undo this impossibility. In that event, common law could once again complement the FDA’s mandate to monitor drug safety across the full range of drugs, rather than just the decreasing portion occupied by brand-name drugs. The procedures set forth in the FDA’s proposed rule would not only eliminate the absurd inconsistency in common-law protections based on the happenstance of whether the patient ingested the generic or brand-name form of the

⁹⁸ 78 Fed. Reg. at 67988-89.

⁹⁹ *Mensing*, 131 S. Ct. at 2593 (Sotomayor, J., dissenting).

¹⁰⁰ Brief for the United States as Amicus Curiae Supporting Resp’ts, *Pliva v. Mensing*, 131 S. Ct. 2567 (2011) (Nos. 09–993, 09–1039, 09–1501) at 26 (U.S. Brief); see also *Wyeth*, 129 S. Ct. at 1203 (“[T]he FDA long maintained that state law offers an additional, and important, layer of consumer protection that complements FDA regulation.”).

¹⁰¹ 555 U.S. at 579.

¹⁰² *Id.* at 574; See also U.S. Brief at 28; Margaret Porter, *The Lohr Decision: FDA Perspective and Position*, 52 Food & Drug L.J. 7, 11 (1997) (article by then-FDA Chief Counsel, stating that “[e]ven the most thorough regulation of a product such as a critical medical device may fail to identify potential problems presented by the product. Regulation cannot protect against all possible injuries that might result from use of a device over time. Preemption of all such claims would result in the loss of a significant layer of consumer protection . . .”).

drug, it would also restore marketplace equality, as both types of manufacturers would face the same potential liability for failures to adequately warn of hazards associated with their products. Thus, restoring the incentive for postmarketing vigilance will result in more up-to-date labeling, leading to fewer injuries, and giving rise to fewer lawsuits than before the decision in *PLIVA*.

II. CONCERNS EXPRESSED ABOUT THE FDA’S PROPOSAL ARE UNFOUNDED.

The agency has proposed to allow ANDA holders to revise labeling to add warnings or other newly acquired safety information through the CBE-0 process. The proposal would fill the existing regulatory gap, thereby ensuring that drug labeling is updated to provide warnings based on new information to protect patient safety. Nonetheless, representatives of the generic industry have raised several concerns about the proposal.

A. The Hatch-Waxman Amendments and Sameness

The Hatch-Waxman Amendments do not bar generic drug manufacturers’ use of the CBE-0 process, as the Supreme Court recognized in *Mensing*. There, the Court considered whether the restrictions imposed by federal law on the ability of generic drug manufacturers to alter labeling preempt state common-law claims against a generic manufacturer based on failure to warn of hazards associated with its product. Looking to the regulatory limitations on ANDA holders’ ability to revise labeling, the Court concluded that “it was impossible for the Manufacturers to comply with both their state-law duty to change the label and their federal law duty to keep the label the same.”¹⁰³ This holding, however, was expressly premised on the operation of current FDA regulations. Specifically, the Court deferred to the FDA’s position that generic manufacturers cannot invoke CBE-0 or PAS procedures to change labeling because doing so would violate the requirement under 21 C.F.R. § 314.94(a)(8)(iii) that generic and brand-name labeling be the same.¹⁰⁴ *Mensing* recognized that *both* “Congress and the FDA retain the authority to change the law and regulations if they so desire.”¹⁰⁵

Further, while the Hatch-Waxman Amendments and FDA approval of an ANDA are premised on the equivalence of the branded drug and generic version, they are not premised on the branded and generic versions being identical. Accordingly, with respect to both ingredients and labeling, the FDA does not require that the branded and generic products be “the same.” Rather, FDA regulations acknowledge that labeling “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.”¹⁰⁶

The FDA’s proposal would add an additional exception to the longstanding list of exceptions to labeling equivalence or “sameness.” The new exception builds on an existing exception to

¹⁰³ *Mensing*, 131 S. Ct. at 2578.

¹⁰⁴ *Mensing*, 131 S. Ct. 2575; *see* U.S. Brief at 16 (“FDA has consistently taken the position that an ANDA holder may not unilaterally change its approved labeling”); *id.* at 17 (“The PAS process also was not available to petitioners to make the labeling change respondents envision.”).

¹⁰⁵ 131 S. Ct. at 2582.

¹⁰⁶ 21 C.F.R. § 314.94(a)(8)(iv); *see also* 21 U.S.C. § 355(j)(2)(v).

“sameness”: Currently, the generic labeling differs from the brand-name labeling during the period between the NDA holder’s submission of a CBE-0 supplement and the FDA’s approval. (Even upon approval, ANDA holders may not be aware that the NDA holder has made a change because they learn of changes via an FDA webpage that is updated *monthly* to reflect only *approved* changes.¹⁰⁷) The proposed rule would allow this exception to apply in the reverse scenario—during the pendency of the ANDA holder’s CBE-0 supplement.¹⁰⁸ When the CBE-0 change is approved, the FDA will apply it to both the RLD and the ANDA holder (and other ANDA holders).¹⁰⁹ Thus, the period during which the branded and generic labeling differ with respect to the new safety information should be comparable to or shorter than the period in which they differ under the current regulatory scheme, under which generic manufacturers cannot make labeling changes to reflect RLD changes until after the review period for CBE-0 changes made by branded companies.

In short, both the FDCA and FDA regulations expressly anticipate and provide for differences between NDA and ANDA labeling. To our knowledge, these exceptions to “sameness” have been uncontroversial. Thus, the FDA, manufacturers, and patient advocates have long accepted that “sameness” is not to be taken literally, but functionally, as a way to implement the concern of the Hatch-Waxman Amendments that generic and brand-name drugs be equivalent. An additional exception that applies only temporarily as a means of expediting the provision of updated safety information to physicians and patients is likewise consistent with Hatch-Waxman.

By giving ANDA holders more responsibility for labeling, the proposed rule also encourages more vigilance, both to monitor adverse events and medical literature to determine when labeling updates are called for and also to monitor the FDA’s labeling webpage for approved (and required) updates for the RLD. The latter is already required, and continuing that already-required monitoring ensures that the proposed rule creates no inconsistencies. Indeed, the proposed rule includes a clear time limit within which ANDA holders must make conforming changes after FDA approval of a CBE-0 supplement, whereas current regulations state no deadline.¹¹⁰ For these reasons, the proposed rule is likely to reduce the period of variations in labeling between generic products and the brand-name products on which they are based.

B. Concern about Physician Confusion

Spokespeople for generic drug manufacturers have expressed concern that the proposed rule would result in inconsistent labeling that will confuse physicians. That concern is unwarranted

¹⁰⁷ FDA Guidance, *supra* note 33. Further, the FDA has not set a specific deadline within which generic drug companies must revise labeling to reflect branded labeling changes after the changes are posted to the FDA webpage. The FDA has stated the timeframe as “at the very earliest time possible” after the brand-name change. *Id.* By comparison, when the FDA has ordered the change, the ANDA holder is expected to make the change within 30 days after the FDA’s written notification that the NDA holder has made the change. *See* FDA, Guidance for Industry, *Safety Labeling Changes—Implementation of Section 505(o)(4) of the Federal Food, Drug, and Cosmetic Act* 11 (July 2013), at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM250783.pdf>.

¹⁰⁸ 78 Fed. Reg. at 67994.

¹⁰⁹ *Id.* 67989-90.

¹¹⁰ 78 Fed. Reg. at 67993.

for several reasons. First, as explained above, under the proposed rule, the period in which labeling of the NDA and ANDA holders would differ will be no longer (and perhaps shorter) than under current regulations. And the FDA has structured the regulation to allow simultaneous review—with simultaneous approval or complete response—of both the ANDA holder’s CBE-0 supplement and a corresponding CBE-0 supplement from the NDA holder for the RLD. After approval of the CBE-0 supplements of the ANDA and corresponding NDA holders, other ANDA holders will be required to submit conforming revisions.¹¹¹ This approach guards against labeling with varied warnings existing beyond a very short period, and, in this regard, the process and period of variation is the same as (or better than) under current regulations.

Second, by giving generic manufacturers the option of making CBE-0 changes, the proposed rule allows those manufacturers to make a CBE-0 revision while the FDA review of another manufacturer’s revision is pending—whether the revision of the brand-name or of a generic manufacturer. That is, unlike under current regulations, generic manufacturers will not have to wait until the FDA approves the brand-name CBE-0 change before it makes a conforming change. As result, labeling for the NDA and ANDAs may be in conformity months sooner than is currently the case.

Third, even where several different generic manufacturers are selling the same drug product, there is no reason to think that the FDA will receive inconsistent labeling revisions. Numerous different newly discovered safety risks are unlikely to come to light for a single drug all at the same time. Where there are several distinct drugs within a single class (for example, Prozac, Zoloft, and Paxil, members of a specific class of antidepressants) sold by different brand-name manufacturers, manufacturers do not each discover different new safety risks all at about the same time. If several manufacturers submit changes at or near the same time, the changes are very likely to address the same risk. In addition, the FDA proposes to post CBE-0 submissions online. This feature of the rule will enable and encourage other ANDA holders to use the same language submitted with the initial supplement.

Lastly, for the years 2009-2010, brand-name manufacturers submitted an average of 182 safety-related CBE-0 supplements per year, and approximately 11 per year for drugs also sold in generic form.¹¹² Although the number would increase under the FDA’s proposed rule, the relatively small number of CBE-0 supplements in relation to the approximately 4,000 approved drugs offers an additional reason why concern about a flood of inconsistent CBE-0 submissions is unwarranted. In the unlikely event that several generic manufacturers submit different CBE-0 supplements at the same time and the FDA sees a risk of confusion, it can promptly review and approve or disapprove each of them, ask manufacturers of that drug not to submit additional updates until the agency has considered those that are pending, or take other appropriate steps to address the matter.

C. Concerns about Over-Warning and Resources

Another objection recently made to the FDA’s proposal is that generic manufacturers will over-warn if allowed to make safety-related revisions. This objection is also unwarranted.

¹¹¹ *Ibid.*

¹¹² FDA Regulatory Impact Analysis, *supra* note 17, at 7, 8.

Although brand-name manufacturers have had the ability to make safety updates for nearly 30 years, over-warning has not been a problem. As the FDA's Associate Director for Policy, Center for Drug Evaluation and Research (CDER), who has led CDER's Office of Regulatory Policy for more than 20 years,¹¹³ has stated: "We rarely find ourselves in situations where sponsors want to disclose more risk information than we think is necessary. To the contrary, we usually find ourselves dealing with situations where sponsors want to minimize the risk information."¹¹⁴ Put simply, the FDA "has not experienced problems with sponsors' use of CBE supplements to over warn."¹¹⁵

In addition, ANDA holders are fully capable of making CBE-0 changes. Mechanically, the procedure already exists, as the CBE-0 process is well-established, and generic manufacturers should already have in place procedures for revising labeling in response to FDA orders and revisions by brand-name manufacturers. Practically, the FDA webpage will facilitate the process. Realistically, many ANDA holders are large companies, including some that also manufacture brand-name drugs and, therefore, have the resources and familiarity with CBE-0 supplements to make label changes promptly and accurately. For instance, leading generics manufacturer Teva Pharmaceutical Industries "rank(s) among the 10 top pharmaceutical companies in the world," boasts a 20 percent share of the U.S. generics market, and has expanded beyond generics into "specialty medicines" and "new therapeutic entities," according to the company's website, while brand-name manufacturers Pfizer Inc. and Novartis Corp. have generics divisions that in 2010 ranked as the third and fifth leading generics companies, respectively.¹¹⁶ More importantly, adverse event reports are the most frequent source of labeling changes.¹¹⁷ These reports are publicly available through the FDA¹¹⁸ and therefore available to all generic manufacturers.

Some representatives of the pharmaceutical industry have suggested that the FDA, not the companies, should initiate labeling changes. The premise of the postmarketing regulatory scheme, however, is that the FDA does not and cannot take primary responsibility for monitoring the thousands of drugs on the market. As the Supreme Court put it: since the FDCA was enacted, "[i]t has remained a central premise of federal drug regulation that the manufacturer bears responsibility for its label at all times."¹¹⁹ This point is borne out in practice: In 2010, manufacturers "initiated 58% of safety-related label changes compared to 42% initiated by the FDA." Although the "FDA initiated most of the boxed warnings (84% versus 16%)," manufacturers initiated 78% of the changes to the adverse reaction section of the labeling.¹²⁰

¹¹³ FDA, *About FDA*, Jane Axelrad, at <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm374540.htm>

¹¹⁴ *FDA Career Staff Objected To Agency Preemption Policies*, United States House Of Representatives, Committee On Oversight And Government Reform, Majority Staff Report 3 (Oct. 2008) (hereafter *FDA Career Staff*).

¹¹⁵ *Ibid.*

¹¹⁶ See Dearment, *Countdown to 2011*, *supra* note 13.

¹¹⁷ Lester, *supra* note 40, at 304.

¹¹⁸ See FDA, *FDA Adverse Event Reporting System*, at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm>.

¹¹⁹ *Wyeth v. Levine*, 555 U.S. at 570-71.

¹²⁰ Lester, *supra* note 40, at 303.

D. Potential for Generic Manufacturer Liability

Finally, although allowing generic manufacturers to use the CBE-0 process would also allow the manufacturers to be held accountable to patients for failure to warn, this accountability does not pose the grave problems suggested by generic drug companies. The companies have argued that the proposed rule, when finalized, will expose them to higher insurance premiums to cover liability risk and that some companies may even go out of business or decline to enter the market. Recent history proves this argument wrong.

Until June 2011, the courts had “almost uniformly ruled that tort claims against generic manufacturers are not preempted,”¹²¹ and many cases were resolved favorably to the plaintiffs. Yet the generic drug industry thrived during this period, capturing 84 percent of the market for prescription pharmaceuticals, as discussed above. Thus, the proposed rule would not create a *new* cost, but one borne by the industry consistently until June 2011 (and still borne by brand-name manufacturers today).¹²²

In any event, generic manufacturers are wrong to assume that they will incur large liability costs if the proposal is finalized. Rather, by giving companies greater ability to make prompt safety updates, the proposed rule should help them avoid liability, as compared to the circumstances prior to June 2011 (a period during which the industry grew exponentially), by helping prevent injuries from occurring in the first place. In short, properly used, the revised rule will reduce injuries and thus actual instances of litigation compared with the pre-*Mensing* regime.

It is important to keep in mind that lawsuits for failure to warn, when meritorious, occur because a patient suffered injury due to the lack of an adequate warning. For example, the FDA approved the acne medicine Accutane in 1982 and approved the generic form in 2002. The drug has a history of causing significant injury requiring labeling revisions—including warnings about birth defects and mental health risks. Despite reports that the drug can cause inflammatory bowel disease, the brand-name company did not add a warning to the labeling. Finally, in 2009, the FDA ordered that an inflammatory bowel disease warning be added to the label. In the meantime, many patients, often teenagers, developed inflammatory bowel disease, requiring surgeries and altering their lives forever. Because only the brand-name drug could effect labeling changes, none of the many patients who received the generic form can seek compensation from the manufacturers for the thousands of dollars of medical expenses they incurred because of the inadequate warnings. And today, this drug is available in generic-form only.¹²³

Of course, the manufacturer is not responsible every time that a patient is injured. Sometimes, the patient should not prevail in court. But sometimes, as with Accutane, the manufacturers, including generic manufacturers, had the information but turned a blind eye. The current system allows generic manufacturers to do that. The result is more injury and more costs,

¹²¹ See *Mensing v. Wyeth*, 588 F.3d 603, 607 (8th Cir. 2009).

¹²² See World Health Organization, *Trade, foreign policy, diplomacy and health: Pharmaceutical Industry* (2014), at <http://www.who.int/trade/glossary/story073/en/> (10 largest drug companies have profit margins of about 30%); see also *id.* (“Companies currently spend one-third of all sales revenue on marketing their products—roughly twice what they spend on research and development.”).

¹²³ PC Report, *supra* note 42, at 11.

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

III. CONCLUSION

The proposed rule is well crafted to fill a safety gap, using existing tools. ANDA holders have an existing duty to maintain both accurate labeling and procedures for the surveillance and reporting of postmarketing adverse drug experiences. Because NDA and ANDA holders share these responsibilities, they likewise should share the authority to make safety changes when new information warrants them.

The proposed rule recognizes generic drugs' significant role in today's pharmaceutical marketplace and is carefully tailored to comply with the FDCA, the needs of patients and physicians, and the resources and expertise of the industry. The rule would increase patient safety, is fully consistent with the sorts of variations between brand-name and generic labeling already built into the regulations, and would not impose burdensome costs on manufacturers. Public Citizen urges the FDA to finalize the proposed rule expeditiously.

Thank you.

/s/ Sidney M. Wolfe, MD
Founder and Senior Advisor, Public Citizen Health Research Group

/s/ Allison M. Zieve
Director, Public Citizen Litigation Group

/s/ Brian Wolfman
Co-Director, Institute for Public Representation,
Georgetown University Law Center