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BEFORE THE COMMITTEE ON ENERGY AND COMMERCE

SUBCOMMITTEE ON HEALTH

UNITED STATES HOUSE OF REPRESENTATIVES

HEARING ON

EXAMINING CONCERNS REGARDING FDA'S PROPOSED CHANGES

TO GENERIC DRUG LABELING

March 3, 2014

Mr. Chairman and Members of the Committee, thank you for inviting me to share with you my views on the Food and Drug Administration's proposed rule addressing supplemental applications proposing labeling changes for approved drugs. I am Director of Public Citizen Litigation Group and General Counsel of Public Citizen, and my work involves both regulatory matters such as FDA regulation and access to courts issues, such as federal preemption of state-law claims. In August 2011, Public Citizen submitted to the FDA a citizen petition asking the agency to authorize generic drug manufacturers to revise product labeling through the procedures available to brand-name manufacturers. In November 2013, the FDA granted the citizen petition in part by issuing the proposed rule.[1]

I am here to speak in strong support of the FDA's proposal, which will bring post-market regulation of generic drugs in line with the realities of the pharmaceutical market today and help ensure that drug labeling provides adequate warnings to patients based on information that comes to light after the drug is on the market. While the objections to the proposal focus on liability, the purpose of the rule is to improve drug safety.

Since 1984, the prescription-drug market has been transformed: Sales of generic drugs have skyrocketed and now constitute the vast majority of all prescriptions filled. This is a good thing. Yet despite considerable changes in the market, FDA regulation of generic labeling has remained substantially unchanged.

In terms of labeling responsibility, generic manufacturers today are in a position similar to that of brand-name companies in 1982, when those companies urged the FDA to adopt the regulation that allows brand-name manufacturers to revise labeling to make safety updates prior to FDA approval of the revision—what we refer to as the "changes being effected" or CBE regulation. Before 1982, the FDA generally required prior approval for all labeling changes.[2] Brand-name manufacturers argued to the FDA that this requirement was unnecessary, took FDA reviewers away from other important work, and caused costly delays. In response, the FDA identified numerous types of changes that manufacturers could make without prior approval, including "[c]hanges that add or strengthen a contraindication, warning, precaution, or statement about an adverse reaction, drug abuse, dependence, or overdosage, or any other instruction about dosage and administration that is intended to improve the safe use of the product."[3] These changes, the FDA said, "would help concentrate the agency's limited resources more on applications for marketing, and would also permit

[1] A copy of the citizen petition is available at http://www.citizen.org/documents/Citizen-Petition-8-26.pdf and attached to my written testimony, along with a 2013 study referred to later in this testimony. *See infra* note 5. These documents set forth in greater detail the reasons why the proposed rule fills an important gap in the regulation of drug safety.

[2] *See* 47 Fed. Reg. 46622, 46634 (1982).

[3] *Id*. at 46635.

pharmaceutical manufacturers to institute certain postmarketing changes sooner,"[4] thereby advancing safety.

The concerns that motivated the FDA to adopt the CBE option in 1982—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 quickly pre-approve safety updates 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 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 drugs. Therefore, today, to fulfill the goal of providing timely labeling updates to physicians and patients, the CBE process must be available to generic, as well as to brand-name, manufacturers. As generic market share increases, the brand-name manufacturer loses incentive to devote resources to post-approval safety monitoring. Given that the FDA cannot monitor all post-approval data by itself, drug safety is threatened when the regulatory and common-law incentives designed to motivate manufacturer diligence weaken with shifting control of market share.

Last summer, Public Citizen compiled a list of drugs for which black-box warnings—reserved for the most serious 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 of the most serious type commonly arise after generics have entered the market, and they underscore the public health imperative of maintaining an incentive for generic manufacturer surveillance for safety.[5] A 2013 article authored jointly by three FDA staff and two academics confirms this result: "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."[6]

This point is particularly important because brand-name manufacturers not only drop to a small market share fairly quickly after introduction of a generic onto the market, but the

[4] *Id*.

[5] Public Citizen, *Generic Drug Labeling: A report on serious warnings added to approved drugs and on generic drugs marketed without a brand-name equivalent* 7-10 (2013), available at http://www.citizen.org/documents/2138.pdf. And attached as an exhibit to this testimony.

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

brand-name manufacturer often stops selling the drug altogether.[7] In fact, a 2012 study by the Generic Pharmaceutical Association notes that, for 45 percent of generics sold, no branded product is currently on the market—that is about two thousand products.[8] Accordingly, in these instances, if generic manufacturers are not actively monitoring and proposing safety updates, no manufacturer is doing so at all.

Our research and the medical literature confirm the findings of a 2010 FDA study 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 product.[9]

It is no answer to say that the FDA does postmarketing surveillance and can order labeling changes. The premise of the postmarketing regulatory scheme 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 Food, Drug, and Cosmetic Act was enacted, "[i]t has remained a central premise of federal drug regulation that the manufacturer bears responsibility for its label at all times."[10] 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.[11]

The concern that the proposed rule would result in confusing or inconsistent labeling is unwarranted. **First**, the FDA has structured the regulation to invite the brand-name manufacturer to submit a revision upon receipt of the generic labeling revision, to allow simultaneous review—with simultaneous approval or other response—of both the generic manufacturer's labeling revision and the corresponding brand-name manufacturer's revision.[12] And the period in which labeling of the brand-name and other generic drugs would differ will be no more than under current regulations (and perhaps less, in light of an aspect of the proposed change that would specify a 30-day period for conforming changes[13]—whereas today, there is not a specified time for conforming changes). This approach guards against labeling with varied warnings existing beyond a short period, and, in this regard, the process is no different than under current regulations. **Second**, there is simply no reason to think that, even where several different generic manufacturers are selling the same drug product, the FDA will receive inconsistent labeling revisions. Numerous different newly

[7] *See* Public Citizen, *supra* note 5, at 12-23.
[8] Generic Pharm. Ass'n, *Generic Drug Savings in the U.S*. at 8 (4th ed. 2012).
[9] 78 Fed. Reg. 67985, 67988 (2013) (proposed rule).
[10] *Wyeth v. Levine*, 555 U.S. 555 (2009).
[11] Lester, *supra* note 6, at 303.
[12] *Id*. at 67990.
[13] 78 Fed. Reg. at 67999 (proposed revision to § 314.70(c)(8)(iv)).

discovered safety risks are unlikely to come to light for a single drug at the same time. We know this because 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, we do not see the manufacturers discovering a variety of new safety risks all at about the same time. If several manufacturers submit changes at or near the same time, the changes are likely to address the same risk—and it will hardly confuse physicians and patients if, for instance, one generic warns that its drug "has been associated with inflammatory bowel disease in patients without a prior history of intestinal disorders," while another warns that "long term use is associated with serious intestinal problems, including ulcerative colitis and Crohn's disease," and a third warns that "patients taking this product should be monitored closely for signs of signs of inflammatory bowel disease." **Third**, while there is no reason to think that it will happen, if several generic manufacturers submit different types of updates at the same time, and the FDA sees a risk of confusion, it can promptly disapprove updates or send a letter to manufacturers of that drug product asking them not to submit additional updates until the agency has considered those that are pending.

Moreover, currently, despite the "sameness" requirements of the Hatch-Waxman Amendments, brand-name and generic labeling often vary, a fact that "stands in stark contrast to the expectations of providers, the FDA, and, more recently, the United States Supreme Court."[14] As a 2012 study by three academic physicians found, there often is significant inconsistency between safety labeling on the brand-name drug and the generic counterpart.[15] While these variations seem to run counter to the regulatory regime, other variations are built into the regulations—such as the listing of different formulations or different allergy warnings or omission of a particular use. 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 Hatch-Waxman's concern that generic and name-brand drugs be equivalent. Adopting 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 the Hatch-Waxman Amendments.

By giving generic manufacturers 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 drug. FDA regulations have long required generic manufacturers to do this monitoring (the same as brand-name companies),

[14] *See* Duke, et al., *Consistency in the safety labeling of bioequivalent medications*, Pharmacoepidemiology and Drug Safety (2012).
[15] *Id.*

and continuing that already-required monitoring ensures that the proposed rule creates no confusion. Indeed, the clear time limits proposed by the agency are likely to ameliorate the current variations in labeling between generic products and their brand-name equivalents.

In addition, generic manufacturers are fully capable of initiating labeling changes. Mechanically, the procedure already exists, as the CBE process is well-established, and generic manufacturers 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 (although not all) generic manufacturers are large companies, including some that also manufacture brand-name drugs and, therefore, have the resources and familiarity with the process to make labeling changes promptly and accurately. For instance, leading generics manufacturer Teva Pharmaceutical Industries "rank(s) among the 10 top pharmaceutical companies in the world" and boasts a 20 percent share of the U.S. generics market, 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.[16] In addition, adverse event reports are the most frequent source of labeling changes.[17] These reports are publicly available through the FDA[18] and therefore available to all generic manufacturers.

Another objection recently made to the FDA's proposal is that, if allowed to make safety-related revisions, manufacturers will over-warn. This objection is also unwarranted. Although brand-name manufacturers have had the ability to make safety updates for more than 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,[19] 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."[20] Put simply, the FDA "has not experienced problems with sponsors' use of CBE supplements to over warn."[21]

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[16] *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.
[17] Lester, *supra* note 11.
[18] *See* FDA, FDA Adverse Event Reporting System, at http://www.fda.gov/Drugs/GuidanceComplianceRegulatory Information/Surveillance/AdverseDrugEffects/default.htm
[19] FDA, About FDA, Jane Axelrad, at http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsand Tobacco/CDER/ucm374540.htm
[20] *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*).
[21] *Id.*

Finally, the generic manufacturers have suggested several economic arguments in opposition to the rule change, based on the fact that they would be open to liability for harm to patients if, after the rule change, they failed to provide adequate warnings about safety risks associated with their products. Specifically, the companies have argued that the proposed rule, when finalized, will increase the cost of generics drugs, that insurers may refuse to insure the companies, and that some companies may even go out of business or decline to enter the market as a result. Although to initiate safety labeling revisions 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. Rather, very recent history proves these theories wrong.

For all but the last three years, generic drug manufacturers *have* faced liability risk because, until the Supreme Court's *PLIVA v. Mensing* decision in June 2011, generic companies *could* be and *were* sometimes sued for failure to warn of risks posed by their products. *No court of appeals had accepted the argument that generic drug manufacturers could not be held accountable for failure to warn*. Thus, the proposed rule would not create a *new* cost, but one borne and managed well by the industry consistently until June 2011—and still borne by brand-name manufacturers today.[22]

Further, as the cost per prescription did not drop after the Supreme Court's decision in 2011, there is no basis for assuming that the cost per prescription will rise in light of the new rule. And the recent industry prediction that insurers might refuse to insure generic drug companies against liability risk is flatly contradicted both by the fact that the companies presumably carried such insurance through June 2011 and the fact that brand-name companies continue to face liability risk, and also to obtain insurance, today.

Moreover, the generic manufacturers are wrong to assume that they will incur large liability costs if the proposal is finalized. Rather, with greater ability to make prompt safety updates, the proposed rule should help avoid liability, as compared to the circumstances prior to June 2011 (a period during which the industry grew exponentially). This is because the rule will help prevent injuries from occurring in the first place.

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. Reports that the drug can cause inflammatory bowel disease appeared throughout that time.

[22] *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.").

Yet the brand-name company did not add a warning to the labeling, although the reports were available for both the brand-name and generic manufacturers to see. Finally, in 2009, the FDA ordered an inflammatory bowel disease warning to be added to the label. In the meantime, many patients, primarily teens, developed inflammatory bowel disease, requiring surgeries and altering their lives forever. Because only the brand-name drug could effect labeling changes, but so many of these patients were prescribed the generic form, none of them 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, which has a history of causing significant injury—ranging from birth defects, to mental health issues, to ulcerative colitis, requiring a series of labeling revisions throughout its history, the most recent one just a few years ago—is available in generic-form only.

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 in the case of Accutane, the manufacturers, including generic manufacturers, had the information but turned a blind eye. The current system is complicit in allowing generic manufacturers to do that. The result is more injury and more costs. Why more costs? Because immunizing the companies from liability does not make the injured patients' costs go away. The medical expenses and lost wages from lost work time still exist; they are carried by the patients, health insurers, and taxpayers, through Medicare or Medicaid. Because the proposed rule will give generic manufacturers the tools and incentive to update safety labeling, any costs of the rule should be offset by cost savings—savings in medical care for the patients who will not be injured because physicians and patients are armed with updated labeling about safety risks.

Finally, while the objections to the proposed rule center on liability, the primary concern should be with safety. The potential for liability is relevant in this regard because it incentivizes manufacturers to take extra care to ensure that their products are as safe as possible. As FDA's Chief Counsel from 1989 through 2001 stated: "FDA product approval and state tort liability operate independently, each providing a significant, yet distinct, layer of consumer protection. FDA regulation of a [product] cannot anticipate and protect against all safety risks to individual consumers."[23] Similarly, the highest official in FDA's new drug review process in 2008 (a time when the FDA was pro-active in revising regulations for the purpose of immunizing manufacturers from liability) wrote: "[M]uch of the argument for why we are proposing to invoke preemption seems to be based on a false assumption that the FDA approved labeling is fully accurate and up-to-date in a real time basis. We know that such an assumption is false."[24] He continued, "[w]e know that many current approved drug labels are

[23] Margaret Jane Porter, *The Lohr Decision: FDA Perspective and Position*, 52 Food & Drug L.J. 7, 11 (1997) (discussing medical device regulation).
[24] *FDA Career Staff*, *supra* note 20, at 2.

out of date and in many cases contain incorrect information (e.g., the overdose section) … [I]t is unwise to suggest that FDA approved labeling is always up-to-date and always contains a full and complete listing of all pertinent risk information."[25]

In short, properly used, the revised rule will improve patient safety, and by reducing injuries should also reduce actual instances of litigation as compared to the years before June 2011.

I would be glad to take questions. Thank you.

[25] *Id.*

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August 29, 2011

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CITIZEN PETITION

This petition is submitted under 21 C.F.R. § 10.30 by Public Citizen, a consumer organization with more than 225,000 members and supporters nationwide, to request that the FDA authorize generic drug manufacturers to revise generic drug labeling through the changes-being-effected (CBE) and prior-approval-supplement (PAS) 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 now constitute the majority of all prescriptions filled. Yet despite considerable changes in the market, FDA regulation of generic labeling has remained substantially unchanged. The regulatory revisions requested here would bring post-market regulation in line with the realities of the pharmaceutical market and help to ensure that drug labeling provides adequate warnings to patients based on information that comes to light after the drug is approved for marketing.

I. ACTIONS REQUESTED

Public Citizen requests that, through notice and comment rulemaking, the FDA amend 21 C.F.R. § 314.70(a) to specify that 21 C.F.R. § 314.70(b) and (c) apply to abbreviated new drug application (ANDA) holders. This amendment would authorize an ANDA holder to change that drug's approved label by filing a supplement through the CBE and PAS procedures. The amendment might also make exceptions to reflect situations in which the agency believes that particular ANDA holders lack an adequate basis to make labeling changes, such as, perhaps, during the first few months after the first ANDA holder enters the market or for an ANDA holder that sells very few prescriptions of a drug (for example, under 1,000 prescriptions per year).

Public Citizen also requests that the FDA amend regulations that permit ANDA approval to be withdrawn if a generic drug's approved labeling differs from that of the

reference listed drug (RLD), *see*, *e.g.*, 21 C.F.R. § 314.150(b)(10), to specify that this regulation does not apply to ANDA holders permitted to supplement labeling through CBE or PAS procedures. Finally, Public Citizen requests that the FDA clarify that *all* ANDA holders are required to report safety concerns to the FDA as soon as they become aware of a clinically significant hazard. Part III, below, contains a more detailed statement of the action requested and proposes language for amended regulations.

II. STATEMENT OF GROUNDS

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. Gen. Pharm. Ass'n, *Savings Achieved Through the Use of Generic Pharmaceuticals 2000-2009* (2010). In 1983, only 35 percent of top-selling drugs with expired patents had generic equivalents; by 1998, nearly all did. Congressional Budget Office, *How Increased Competition From Generic Drugs Has Affected Prices and Return in the Pharmaceutical Industry*, at xii (1998). And when generics compete, they typically capture a significant part of market share and profit. *See* Congressional Budget Office, *Research and Development in the Pharmaceutical Industry* 16-17 (2006). As of 2010, 90 percent of prescriptions for drugs with generic versions were filled with a generic rather than the brand-name, HHS, *ASPE Issue Brief: Expanding the Use of Generic Drugs* 3-4 (2010), a development spurred by state laws authorizing pharmacists to substitute generic drugs when filling prescriptions. *See* Thomas P. Christensen et al., *Drug Product Selection: Legal Issues*, 41 J. Am. Pharm. Ass'n 868 (2001). Some states have gone further and now mandate generic substitution where available. William H. Shrank et al., *State Generic Substitution Laws Can Lower Drug Outlays Under Medicaid*, 29 Health Affairs 1383 (July 2010). From 2009 to 2010 alone, generic prescriptions' share increased by 4 percent to reach 78 percent of all U.S. prescriptions. IMS Institute for Healthcare Informatics, *The Use of Medicines in the United States: Review of 2010* 11, 15, 22 (April 2011) (IMS Report). In 2010, generics captured more than 80 percent of the market within six months of expiration of the brand-name's patent (as compared to 55 percent in 2006). *Id.* at 21.

Generic manufacturers' market growth has been accompanied by an expansion in their profit margins and research capabilities. Contrary to popular belief, obtaining FDA approval for a generic drug remains a substantial undertaking that requires a significant investment of scientific expertise and research funding. *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."). Generic manufacturers accordingly spend millions of dollars annually on research and development. *See, e.g.*, Teva Pharm. Indus. Ltd, Annual report 2009, at 48 (2010),

available at http://www.tevapharm.com/pdf/teva20F2009.pdf (noting that in 2009 Teva Pharmaceuticals spent approximately 63 percent of a total $802 million in R&D expenses on generic R&D). In some cases, brand-name and generic R&D overlap. *See*, *e.g.*, *id*. at 11. For example, two of the top five generic manufacturers are also divisions of major brand-name manufacturers with well-known new drug research programs (Sandoz and Greenstone, which are divisions respectively of Novartis and Pfizer). *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. As a group of health policy experts and professors of pharmaceutical regulation recently stated: "Our own analysis of FDA data indicates 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 approval." 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). Another study reported that, in 2009, 32 percent of 4,318 unique drug molecules were sold solely as generics. Generic Pharm. Ass'n, *Savings Achieved Through the Use of Generic Pharmaceuticals 2000-2009*, at 7 (2010).

B. POST-APPROVAL MONITORING IS ESSENTIAL TO THE SAFETY OF DRUGS AND IS A SHARED RESPONSIBILITY OF THE FDA AND MANUFACTURERS.

The importance of post-approval monitoring for drug safety is well-recognized. As two scholars recently 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.

Catherine D. DeAngelis & Phil B. Fontanarosa, *Prescription Drugs, Products Liability, and Preemption of Tort Litigation*, 300 J. Am. Med. Ass'n 1939, 1939 (2008). The limitations in pre-approval testing are especially salient when a drug's risks are relatively rare or have long latency periods—forms of risk that the FDA approval process is not designed to uncover. 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, 483 (2008). Examples of drugs whose substantial risks were only discovered post-approval abound in the medical literature. *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). In particular, off-label uses, some of which become popular after a generic option is on the market, may lead to unforeseen side effects. *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 name-brand 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.

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." 129 S. Ct. 1187, 1202 (2009) (footnote omitted). 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." *Id.* at 1197-98. 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) to repeatedly express concern about post-approval drug safety monitoring. *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* Kessler & Vladeck, *A Critical Examination*, 96 Geo. L.J. at 485 (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").

All manufacturers—brand-name and generic—must therefore comply with an extensive set of regulations designed to ensure the post-approval safety of their drugs. 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, postmarketing epidemiological/surveillance studies, reports in the scientific literature, and unpublished scientific papers." 21 C.F.R. § 314.80(b) (rendered applicable to ANDA holders by 21 C.F.R. § 98(a)). Any report of a "serious and unexpected" drug experience, whether foreign or domestic, must be reported to the FDA within 15 days and must be promptly investigated by the manufacturer. 21 C.F.R. § 314.80(c)(1)(i-ii). Most other adverse event reports must be submitted quarterly for three years after the application is approved and annually

thereafter. 21 C.F.R. § 314.80(c)(2)(i). These periodic reports must include "a history of actions taken since the last report because of adverse drug experiences (for example, labeling changes or studies initiated)." 21 C.F.R. § 314.80(c)(2)(ii). 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 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." 21 C.F.R. § 201.57(c)(6)(i) (implementing 21 U.S.C. § 352(f)(2), which provides that a drug lacking "adequate warnings" is misbranded).

Brand-name manufacturers may seek to change their approved labels by filing a supplemental application. 21 C.F.R. § 314.70. A supplemental application must satisfy all regulatory requirements that apply to original applications. *See* 21 C.F.R. § 314.3(b). Although some label changes require prior FDA approval—obtained through a PAS, 21 C.F.R. § 314.70(b)—other changes are brought to FDA's attention "at the time the applicant makes [the] change" through a CBE supplement. 21 C.F.R. § 314.70(c). CBE 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." 21 C.F.R. § 314.70(c)(6)(iii)(A).

Although by their terms the PAS and CBE regulations would seem to apply to both generic and brand-name manufacturers, *see also* 21 C.F.R. § 314.97 (requiring ANDA holders to comply with "requirements [applicable to NDA holders] regarding the submission of supplemental applications"), the FDA has stated that the PAS and CBE processes are not available to generic manufacturers. Instead, the FDA has explained that under current regulations, ANDA holders must generally abide by a "sameness" requirement to keep their label "the same as the labeling of the reference listed drug [RLD]." 21 C.F.R. § 314.94(a)(8)(iii); *see also* 21 C.F.R. § 314.105(c). At the same time, recognizing that there may be reasons to deviate from the sameness requirement, FDA regulations make exceptions for certain types of information. *See id.* § 314.94(a)(8)(iv).[1]

The FDA recently addressed the operation of its post-approval labeling regulations in its amicus brief in *PLIVA v. Mensing*. In that case, the Supreme Court considered whether the restrictions imposed by federal law on the ability of generic drug manufacturers to alter labeling preempts 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

[1] For a fuller discussion of brand-name and generic drug labeling, see, *e.g.*, Brief for the United States as Amicus Curiae Supporting Resp'ts, *PLIVA, Inc. v. Mensing*, 131 S. Ct. 2567 (2011) (Nos. 09–993, 09–1039, 09–1501) (U.S. Brief).

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

Specifically, the Court deferred to the FDA's position that generic manufacturers cannot invoke CBE 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 name-brand labeling be the same. *PLIVA*, 131 S. Ct. 2575; s*ee* U.S. Brief 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."). The FDA's position was based in part on a 1992 Federal Register notice in which the agency had stated that "an ANDA holder wishing to add a warning should furnish adequate supporting information to FDA, which would then determine whether the labeling for all drugs should be modified." U.S. Brief 17. The Court also deferred to the FDA's view that generic manufacturers cannot unilaterally send a "Dear Doctor" letter. *PLIVA*, 131 S. Ct. 2576

C. GENERIC MANUFACTURERS' LACK OF RESPONSIBILITY FOR ENSURING THE POST-APPROVAL ADEQUACY OF PRODUCT LABELING THREATENS PATIENT SAFETY.

The FDA's position on the inapplicability of 21 C.F.R. § 314.70 to ANDA holders, and the Supreme Court's recent decision in *PLIVA*, which turns on the limitations of the regulatory scheme, threaten the safety of prescription drugs, and accordingly, pose unnecessary risks to patients.

First, as explained above, generics compete effectively with out-of-patent brand-name drugs, making prescription drugs more affordable. Yet while their market shares have increased, the regulatory system has not adjusted to compel generic manufacturers to shoulder responsibility commensurate with their status as major market players. At the same time, the rise of generics has weakened incentives for brand-name manufacturers to remain actively engaged in the market for their products after losing patent protection.

Under the product liability law of many states, the brand-name company cannot be held liable drug for harm caused by inadequate labeling where the injured patient took a generic form of the drug. Jim Beck & Mark Hermann, *Scorecard: Non-Manufacturer, Brand Name Defendants in Generic Drug Cases*, Drug and Device Law Blog (Nov. 12 2009), *available at* http://druganddevicelaw.blogspot.com/2009/11/scorecard-non-manufacturer-name-brand. html (collecting cases). When more than 75 percent of all prescriptions are filled by generic versions, this legal reality further diminishes the name-brand manufacturer's incentive to be vigilant and to take the time and expense to submit a CBE or PAS.

These developments collectively give rise to a safety problem: As generic market share increases, the brand-name manufacturer loses incentive to invest resources in post-approval safety monitoring, while generic manufacturers face no concomitant increase in incentive and have no authority to update labeling. Given that the FDA cannot monitor

all post-approval data by itself, drug safety is threatened when the regulatory and common-law incentives designed to motivate manufacturer diligence weaken with shifting control of market share.

The current system is also illogical. As noted earlier, the FDA has recently interpreted the "sameness" requirement under 21 C.F.R. § 314.94(a)(8)(iii) to preclude generic-initiated changes to the label through a CBE or PAS supplement. As a result, current regulations prevent generic manufacturers from providing physicians and patients with updated safety information in light of newly discovered risks. The generic manufacturers are only able to report concerns to the FDA. Yet, as discussed above, those manufacturers frequently control most of a drug's market share and make the most profit from that drug. Even more important, because of their market share, they are likely the main recipients of adverse event reports, may be best informed regarding risks unique to off-label use, 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 and PAS procedures to revise labeling. Once a manufacturer has achieved a certain market share, it should be given the tools to share responsibilities for drug safety and labeling.

Regulatory changes to correct this gap would not impose an obligation beyond the capacity of generic manufacturers. It is our understanding that, under current regulations, a generic manufacturer is designated by the FDA to maintain the label of a drug when the name-brand manufacturer of that drug withdraws from the market. This procedure manifests the FDA's confidence in the ability of generic manufacturers to perform ongoing pharmacovigilance duties—which makes sense, given their substantial scientific and financial resources, as well as the effort they must already invest to comply with post-approval safety regulations.

Second, as discussed above, in *PLIVA*, the Supreme Court held that because generic manufacturers cannot satisfy state common-law duties to amend the drug's label while complying with FDA regulations, those state-law duties were preempted.

The dissent in *PLIVA* noted (and the majority did not disagree) that the Court's holding produces "absurd consequences." 131 S. Ct. at 2592. First, it threatens drug safety by creating a "gap in the parallel federal-state regulatory scheme." *Id.*; *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."). Second, 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—deviates from the "sameness" principle central to Hatch-Waxman by distinguishing generics in a crucial respect: "Consumers of brand-name drugs can sue manufacturers for inadequate warnings; consumers of generic drugs cannot." *PLIVA*, 131 S. Ct. at 2593 (Sotomayor, J., dissenting). The FDA expressed similar concerns in its amicus brief to the Court, noting that generic manufacturers "argue that they enjoy a free pass accorded to virtually no other manufacturer regarding product labeling—in the field

of drugs or otherwise." U.S. Brief 26. In addition, the outcome is in tension with generic substitution laws, as they encourage or even require that prescriptions be filled with generic drugs when possible, but patients' inability to hold generic manufacturers accountable for inadequate labeling (whether the inadequacy is specific to a hazard associated with that generic or applies to the drug more generally) provides incentive for patients to request the brand-name drug instead of the generic. This outcome is also directly contrary to the objective of Hatch-Waxman.

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 premise that manufacturers, not the FDA, bear primary responsibility for their drug labeling at all times.

129 S. Ct. at 1202. State-law remedies thus "further consumer protection by motivating manufacturers to produce safe and effective drugs and to give adequate warnings." *Id*. at 1200; *see also* 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 . . . ."). Post-*PLIVA*, preemption of common-law claims against generic manufactures will strip a vast portion of the market of these safeguards.

Generic manufacturers' immunity from state common-law suits is contingent on the 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 PAS and CBE 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 action requested in this petition 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 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.

III. DETAILED DESCRIPTION OF REQUESTED ACTION

"[T]he FDA has no 'formal regulation' establishing generic drug manufacturers' duty to initiate a label change, nor does it have any regulation setting out that label change process." *PLIVA*, 131 S. Ct. at 2582 n.9 (quoting U.S. Brief 20-21). Filling this regulatory gap will help to ensure that drug labeling is updated to provide warnings based on new information to protect patient safety. Accordingly, FDA regulations should be revised to allow ANDA holders to use the PAS and CBE procedures. The FDA should also clarify the view, first articulated in its 1992 regulations implementing the Hatch-Waxman Amendments, *see* 57 Fed. Reg. 17950, 17961 (1992), that all ANDA holders have a duty to report safety concerns to the FDA.

Our proposal would authorize all ANDA holders to use the CBE and PAS procedures. As mentioned above (at p.2), within six months of patent expiration, the brand-name manufacturer's market share drops to twenty percent or less. At that point, to continue to rely solely on a single manufacturer serving a minority of the market for a particular drug is neither required by Hatch-Waxman nor the best way to protect patients. We recognize, however, that the FDA may want to carve out exceptions. For example, the agency may want to consider an exception for the first few months that the first ANDA holder of a particular drug enters the market, or for an ANDA holder that sells few prescriptions of a particular drug and is not in a position to identify previously unknown risks or labeling deficiencies based on real-world use. Any exceptions could be added to our proposed 21 C.F.R. § 314.70(a)(7). At the same time, for all generic manufacturers, we urge the FDA strongly to reiterate the manufacturers' obligation to inform the FDA whenever the manufacturer becomes aware of information suggesting an association between the product and a hazard not adequately disclosed on the labeling.

Specifically, we suggest the following revisions (current regulations in standard type, additions in italics):

21 C.F.R. § 314.70(a)

(7) *The supplement procedures specified in paragraphs (b) and (c) of this section may be employed by an ANDA holder.*

21 C.F.R. § 314.150(b)(10)

(b) FDA may notify the applicant, and, if appropriate, all other persons who manufacture or distribute identical, related, or similar drug products as defined in § 310.6, and for a new drug afford an opportunity for a hearing on a proposal to withdraw approval of the application or abbreviated new drug application under section 505(e) of the act and under the procedure in § 314.200, if the agency finds:

(10) That the labeling for the drug product that is the subject of the abbreviated new drug application is no longer consistent with that for the listed drug referred to in the abbreviated new drug application, except for differences approved in the abbreviated new drug application or those differences resulting from:

(i) A patent on the listed drug issued after approval of the abbreviated new drug application; or

(ii) Exclusivity accorded to the listed drug after approval of the abbreviated new drug application that do not render the drug product less safe or effective than the listed drug for any remaining, nonprotected condition(s) of use.

(iii) Changes in the ANDA holder's drug product labeling made pursuant to the "prior approval supplement" or "changes being effected" supplement procedures, as applicable to ANDA holders under 21 C.F.R. § 314.70(a)(7).

21 C.F.R. § 201.57(c)(6)(i)(A)

(i) General. This section must describe clinically significant adverse reactions (including any that are potentially fatal, are serious even if infrequent, or can be prevented or mitigated through appropriate use of the drug), other potential safety hazards (including those that are expected for the pharmacological class or those resulting from drug/drug interactions), limitations in use imposed by them (e.g., avoiding certain concomitant therapy), and steps that should be taken if they occur (e.g., dosage modification). The frequency of all clinically significant adverse reactions and the approximate mortality and morbidity rates for patients experiencing the reaction, if known and necessary for the safe and effective use of the drug, must be expressed as provided under paragraph (c)(7) of this section. In accordance with §§ 314.70 and 601.12 of this chapter, the labeling 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. A specific warning relating to a use not provided for under the "Indications and Usage" section may be required by FDA in accordance with sections 201(n) and 502(a) of the act if the drug is commonly prescribed for a disease or condition and such usage is associated with a clinically significant risk or hazard.

A. NDA holders and ANDA holders authorized under 21 C.F.R. § 314.70(a)(7) to use the procedures set forth in 21 C.F.R. § 314.70 (b) and (c) may satisfy this provision's requirement that labeling 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, even if a causal relationship has not been definitely established, using the procedures set forth in 21 C.F.R. § 314.70 (b) and (c).

B. Whether or not authorized to effect labeling changes under 21 C.F.R. § 314.70(a)(7), an ANDA holder that becomes aware of reasonable evidence of a causal association of a drug with a significant hazard (even if a causal

relationship has not been definitely established) must promptly inform and provide such evidence to the FDA.[2]

IV. ENVIRONMENTAL IMPACT

The actions requested in this petition will have no significant effect on the human environment.

V. CERTIFICATION

To the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies and includes representative data and information known to the petitioner that are unfavorable to the petition.

_____
Sidney M. Wolfe, MD
Director, Public Citizen Health Research Group

_____
Allison M. Zieve
Director, Public Citizen Litigation Group

_____
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Co-Director, Institute of Public Representation,
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[2] The amendment to 21 C.F.R. § 201.57(c)(6)(i)(A) would be necessary only if the FDA makes exceptions to the general rule allowing ANDA holders to use the CBE and PAS procedures.

June 2013

www.citizen.org

Generic Drug Labeling

A report on serious warnings added to approved drugs and on generic drugs marketed without a brand-name equivalent

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Executive Summary

Federal law designed to make it easier for generic drugs to gain marketing approval has been hugely successful. Today, the majority of prescriptions filled in the United States are filled with generic drugs, making prescription drugs more affordable for patients.

Although the generic equivalent of a prescription drug cannot enter the market until several years after the brand-name drug is approved for marketing, serious safety hazards often are not identified until a product has been used for many years, including after generic market entry. Reviewing the period January 2008 to March 2013, 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 underscore the public health imperative of maintaining an incentive for generic manufacturer surveillance of safety concerns.

Moreover, competition from generics frequently leads the brand-name manufacturer to cease production of the brand-name drug. For those drugs, patients and physicians cannot rely on the brand-name manufacturer to monitor reports of adverse effects and update the labeling. Based on the *Orange Book*, a publication of the Food and Drug Administration that lists all drugs approved on the basis of safety and effectiveness, we compiled a list of hundreds of drugs for which only generic versions are currently sold. If manufacturers are correct that, even after the brand-name manufacturer has withdrawn its product from the market, not even the leading generic manufacturer can revise labeling except as directed by the FDA, then no manufacturer is responsible for ensuring the adequacy of labeling for these drugs.

In sum, new serious risks to patients are sometimes identified years after a drug enters the market, making a drug's longevity no guarantee of safety, and hundreds of generic drugs are sold without a currently marketed brand-name equivalent. These facts make generic drug manufacturers' inability under current regulations to update the labeling of their products a threat to the safety of prescription drugs, creating unnecessary risks to patients.

Introduction

In the years since passage of the Drug Price Competition and Patent Term Restoration Act of 1984,[1] 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.[2] In 2011, nearly 80 percent of prescriptions filled in the United States were filled with generic drugs.[3] And because generic drugs are less expensive, when consumers have the option to choose a generic or a brand-name drug, they select generic drugs as much as 94 percent of the time.[4]

Although generics dominate the market for prescription drugs, the regulatory system imposes labeling restrictions on generic drug manufacturers that do not exist for brand-name manufacturers. Specifically, current U.S. Food and Drug Administration ("FDA") regulations do not permit a generic drug manufacturer to alter its product's labeling, except to mimic a change made by the brand-name equivalent or ordered by the FDA. This restriction creates a safety gap for patients because manufacturers with a large stake, even the largest stake, in the product have no responsibility for the adequacy of its labeling. The gap becomes even more troubling after the brand-name manufacturer stops selling the drug, as often happens within a few years after generics enter the market.

In addition, in light of the generic manufacturer's lack of responsibility for product labeling, a patient injured because a generic manufacturer failed to warn of a serious risk or provided unclear or misleading instructions for use is unable to seek compensation from the manufacturer.[5] This release from liability diminishes the incentive to be vigilant about product hazards and eliminates the incentive to request labeling changes in response to new evidence.

Although the generic equivalent of a prescription drug cannot enter the market until the patent on the originator product and marketing exclusivities have expired, serious safety hazards often are not identified until a product has been used for many years, including after generic market entry. Indeed, in some instances, safety warnings have been added to drugs more than 50 years after the products came to market. Moreover, competition from generics frequently leads the brand-name manufacturer to cease production of the brand-

[1] Pub. L. No. 98-417, 98 Stat. 1585.

[2] Generic Pharmaceutical Ass'n, *Savings Achieved Through the Use of Generic Pharmaceuticals 2000-2009* (2010).

[3] Generic Pharmaceutical Ass'n, *Generic Drug Savings in the U.S.* at 2 (4th ed. 2012), at http://bit.ly/11rkpz4.

[4] *Ibid*.

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

name drug. For those drugs, patients and physicians plainly cannot rely on the brand-name manufacturer to monitor reports of adverse effects and update the labeling.

Although these two points—late-discovered safety hazards and drugs sold only in generic form—have been cited in discussions about the wisdom of the FDA restrictions, specific information had not been compiled. This report attempts to provide that information.

Labeling Changes To Approved Drugs

When the FDA approves a drug for marketing, it approves the drug's labeling as well.[6] Even after approval, however, FDA regulations require drug labeling to include up-to-date information about hazards associated with a particular drug.[7] Brand-name manufacturers may seek approval for revised labeling in one of two ways: the "changes-being-effected" (CBE) and "prior-approval supplement" (PAS) processes.

The CBE process allows brand-name drug manufacturers to make certain changes to labeling with concurrent notice to the FDA, including changes to strengthen warnings or contraindications and to clarify instructions for use.[8]

The PAS process is used for significant changes to the product, the production process, quality controls, or other aspects of manufacturing that have "a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the product."[9] Any such change requires FDA approval prior to distribution of the product.[10]

Brand-name manufacturers can also inform doctors and other health care professionals about newly discovered safety concerns by sending "Dear Health Care Professional" letters, which are considered part of drug labeling under federal regulations.[11]

None of these options for revising labeling are available to generic manufacturers, according to current FDA regulations. Instead, generics can revise labeling only to mimic a change made by the brand-name manufacturer or as directed by the FDA.[12]

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[6] "Labeling" includes the label itself and all other written or graphic material on or accompanying the product. 21 U.S.C. § 201(m).

[7] 21 C.F.R. § 201.59.

[8] 21 C.F.R. § 314.70(c)(6)(iii).

[9] 21 C.F.R. § 314.70(b).

[10] *Ibid*.

[11] 21 U.S.C. § 321(m); 21 C.F.R. § 202.1(l)(2).

[12] In some instances, after the brand-name drug manufacturer stops selling the drug for reasons other than safety and effectiveness, the FDA will designate a generic version of the drug (usually the market leader) as the "reference listed drug" (RLD), making that generic drug the standard for bioequivalence and labeling to which other generics seeking to enter the market are compared. 21 C.F.R. § 314.3; 57 Fed. Reg. 17950, 17958

Serious Warnings Added After Generics Enter Market

Inadequacies in a drug's labeling, including safety issues, often do not emerge until after the drug has been on the market for a significant period of time. As one study found, "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."[13]

For especially serious risks, particularly those that may lead to death or serious injury, the FDA may require that the information be presented in a box.[14] A boxed warning, sometimes called a black box warning, is reserved for the most serious contraindications and warnings.

The following examples illustrate the severe risks set forth in boxed warnings that were added many years after approval of a drug and introduction of a generic equivalent onto 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.[15] It is approved for several indications, including to treat 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 2 years old.[16] The boxed warning was added after the brand-name manufacturer reported cases of respiratory depression, including fatalities, in children under 2.[17] Phenergan was later discontinued but generic versions of promethazine are still available.[18] 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.[19]

(1992). FDA guidance and regulations do not directly address whether a generic RLD may use the CBE and PAS processes.

[13] Karen E. Lasser, et al., *Timing of New Black Box Warnings and Withdrawals for Prescription Medications,* 287 Journal of the American Medical Association 2215, 2218 (2002).

[14] 21 C.F.R. § 201.57.

[15] FDA, Drugs@FDA, Phenergan, at http://1.usa.gov/15j0qTr.

[16] FDA, Drugs@FDA, Phenergan, at http://1.usa.gov/12OIfEt; FDA, Drugs@FDA, Promethazine Hydrochloride, Label as approved on 11/08/2004, at http://1.usa.gov/156OQPt.

[17] FDA, Drugs@FDA, Promethazine Hydrochloride (ANDA # 004372), Label and Approval History, at http://1.usa.gov/11z19gS (2000 label).

[18] FDA, Drugs@FDA, Phenergan Therapeutic Equivalents, at http://1.usa.gov/12OIJKY.

[19] FDA, Information for Healthcare Professionals - Intravenous Promethazine and Severe Tissue Injury, Including Gangrene (Sept. 16, 2009), at http://1.usa.gov/vGlI7.

- Metoclopramide hydrochloride, sold under the brand name Reglan and other names, was approved to treat gastrointestinal issues in three dosage forms: an injectable formulation approved in 1979, a tablet approved in 1980, and an oral solution approved in 1983.[20] 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.[21] 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.[22] When the FDA announced the warning in 2009, the agency estimated that more than 2 million Americans were taking products that contained metoclopramide hydrochloride.[23]

- 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 pharmaceuticals in the United States.[24] 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.[25] At the request of the FDA, manufacturers removed Darvon and Darvocet 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."[26]

- Pemoline was approved by the FDA in 1975 under the brand name Cylert to treat attention deficit hyperactivity disorder.[27] 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.[28] By December 1998, a total of 15 cases had been identified, a

[20] FDA, Drugs@FDA, Reglan, at http://1.usa.gov/ZZZ24h.

[21] FDA, *Metoclopramide-containing drugs* (Feb. 26, 2009), at http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumaNMedicalProducts/ucm106942.htm.

[22] *Ibid.*

[23] FDA, *FDA requires boxed warning and risk mitigation strategy for Metoclopramide-containing drugs* (Feb. 26, 2009).

[24] 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.

[25] FDA, *FDA Takes Action on Darvon and Other Pain Medications* (July 14, 2009), at http://1.usa.gov/97BMt.

[26] FDA, *Propoxyphene: Withdrawal – Risk of Cardiac Toxicity* (Nov. 19, 2010), at http://1.usa.gov/byZgN1.

[27] FDA, Drugs@FDA, Cylert, at http://1.usa.gov/16pMIF.

[28] FDA, Drugs@FDA, Cylert Label and Approval History, Labeling Revision 7 (Dec. 12, 1997), at http://1.usa.gov/ZxtOoF; FDA, Drugs@FDA, Cylert, Label and Approval History, Control Supplement 12 (Sept. 9, 1996), at http://1.usa.gov/YaUWJ3.

much higher rate than expected in the general population.[29] Of these, 12 resulted in death or required a liver transplant.[30] In 1999-2001, the FDA approved several generic versions of the drug.[31] The brand-name manufacturer removed the drug from the market in 2005, and no branded or generic version is currently available.[32]

- Fluoxetine hydrochloride, approved by the FDA as Prozac[33] in 1987, is prescribed to treat depression and other serious psychological disorders.[34] In 2004, citing heightened risk of suicide in children and adolescents, the FDA directed the manufacturers of all selective serotonin reuptake inhibitor (SSRI) anti-depressants, including fluoxetine, to revise the labeling to include a black box warning.[35] That warning was later extended to adults under 25 who were prescribed an SSRI.[36] Fluoxetine remains on the market today in both brand-name and generic form. [37]

- Haloperidol is an antipsychotic drug approved by the FDA in 1967 as brand name Haldol.[38] 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.[39] 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.[40]

We undertook to assess the quantity of significant labeling changes made after a generic drug came on the market. Limiting the research to changes made from January 2008 through March 2013, and to changes consisting of a new boxed warning, we compiled a list

[29] FDA, Drugs@FDA, Cylert Label and Approval History, Label as approved on 11/21/2003, at http://1.usa.gov/ZTuVhV.
[30] *Ibid*.
[31] FDA, Drugs@FDA, Pemoline, at http://1.usa.gov/189Zzag.
[32] Abbott Laboratories, Dear Prescriber Letter (May 2005), at http://1.usa.gov/189ZymQ; Drugs@FDA, Pemoline, at http://1.usa.gov/189Zzag.
[33] The same new drug application submitted for Prozac and approved in 1987 (NDA #018-936) also supports marketing of the drug under the brand name Sarafem. FDA, Drugs@FDA, Sarafem, at http://1.usa.gov/16pMIF.
[34] FDA, Drugs@FDA, Fluoxetine Hydrochloride 1, at http://1.usa.gov/11UpUof.
[35] FDA, *Suicidality in children and adolescents being treated with antidepressant medications* (Oct. 15, 2004), at http://1.usa.gov/yjXP1G.
[36] FDA, *Antidepressant use in children, adolescents, and adults* (May 2, 2007), at http://1.usa.gov/lXD4C.
[37] FDA, Drugs@FDA, Fluoxetine, at http://1.usa.gov/12OY4v1; FDA, Drugs@FDA, Fluoxetine Hydrochloride, at http://1.usa.gov/11SPOdi.
[38] FDA, Drugs@FDA, Haldol (NDA 015-923), Label at http://1.usa.gov/18f0co.
[39] FDA, *Information for HealthCare Professionals: Haloperidol (marketed as Haldol, Haldol Decanoate and Haldol Lactate*) (Sept. 2007), at http://1.usa.gov/wfODV.
[40] FDA, *Information for Healthcare Professionals: Conventional Antipsychotics* (June 16, 2008), at http://www.fda.gov/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/ucm124830.htm.

of boxed warnings added after the generic equivalent entered the market. In the table below, we indicate the year of the brand-name approval, the year of the boxed warning, and whether the brand-name drug and/or the generic drug is still being sold.

Table 1 does not include any warning, regardless of severity, that was not added as a boxed warning and does not include any other type of significant change, such as a change to the instructions in the precautions or directions for use.

Table 1: Drugs with New Black Boxed Warnings Added after Generic Version Entered Market (January 2008 - March 2013)[41]

Generic Name	Original Brand Name	Year of Approval	Current Availability	Year of New Boxed Warning	Years from Approval to New Boxed Warning
Ciprofloxacin (tablets)	Cipro	1987	Generic and Branded	2008, 2011	21, 24
Ofloxacin (tablets)	Floxin	1990	Generic Only	2008, 2011	18, 21
Clozapine HCL	Clozaril	1989	Generic and Branded	2008	19
Haloperidol (injectable)	Haldol	1971	Generic and Branded	2008	37
Molindone Hydrochloride (tablets)	Moban	1974	Discontinued	2008	34
Thiothixene (capsules)	Navane	1967	Generic and Branded	2008	41
Thiothixene Hydrochloride (concentrate)	Navane	1970	Discontinued	2008	38
Risperidone (tablets)	Risperdal	1993	Generic and Branded	2008	15
Clindamycin (injection in 5% dextrose)	Cleocin Phosphate	1989	Generic and Branded	2008	19
Fentanyl	Duragesic	1990	Generic and Branded	2008, 2012	18, 22

[41] Table 1 was compiled using information available from FDA, Drug Safety Labeling Changes, at http://1.usa.gov/ZTvus5, and FDA, Drugs@FDA, at http://1.usa.gov/8man7w. Information concerning two drugs, Phenergan and Darvon/Darvocet, is also based on the sources cited *supra* at notes 16-19 and 24-26. Information on codeine is based on FDA, *FDA Drug Safety Communication: Safety review update of codeine use in children; new Boxed Warning and Contraindication on use after tonsillectomy and/or adenoidectomy*, (Feb. 2013), at http://www.fda.gov/Drugs/DrugSafety/ucm339112.htm.

Generic Name	Original Brand Name	Year of Approval	Current Availability	Year of New Boxed Warning	Years from Approval to New Boxed Warning
Fentanyl Citrate	Actiq	1998	Generic and Branded	2009	11
Clindamycin Hydrochloride (capsules)	Cleocin HCL	1970	Generic Only	2009	39
Bupropion Hydrochloride	Wellbutrin	1985	Generic and Branded	2009	24
Bupropion Hydrochloride	Zyban	1997	Generic and Branded	2009	12
Metoclopramide (tablets)	Reglan	1980	Generic and Branded	2009	29
Metoclopramide (injectable)	Reglan	1979	Generic and Branded	2009	30
Fludarabine Phosphate	Fludara	1991	Generic Only	2009	18
Mitoxantrone HCL	Novantrone	1987	Generic Only	2009	22
Promethazine	Phenergan	1951	Generic Only	2009	58
Propoxyphene	Darvon / Darvocet	1957	Discontinued	2009	52
Perindopril Erbumine	Aceon	1993	Generic and Branded	2010, 2012	17, 19
Ramipril (capsules)	Altace	1991	Generic and Branded	2010	19
Leflunomide	Arava	1998	Generic and Branded	2010	12
Propylthiouracil (tablets)	Propylthiouracil	1947	Branded Only	2010	63
Captopril	Capoten	1981	Generic and Branded	2011	30
Fosphenytoin Sodium	Cerebyx	1996	Generic Only	2011	15
Phenytoin (injectable)	Dilantin	1956	Generic Only	2011	55

Generic Name	Original Brand Name	Year of Approval	Current Availability	Year of New Boxed Warning	Years from Approval to New Boxed Warning
Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate	Fioricet with Codeine	1992	Generic and Branded	2011	19
Pentazocine Hydrochloride, and Acetaminophen	Talacen	1982	Generic Only	2011	29
Azathioprine (tablets)	Imuran	1968	Generic and Branded	2011	43
Azathioprine sodium (injectable)	Imuran	1974	Generic Only	2011	37
Rosiglitazone Maleate	Avandia	1999	Generic and Branded	2011	12
Mycophenolate Mofetil (capsules)	CellCept	1995	Generic and Branded	2012	17
Mycophenolate Mofetil (tablets)	CellCept	1997	Generic and Branded	2012	15
Methadone Hydrochloride	Dolophine	1947	Generic and Branded	2012	65
Methadone Hydrochloride (oral solution)	Methadone Hydrochloride	1981	Generic Only	2012	31
Methadone Hydrochloride (oral concentrate)	Methadone Hydrochloride	1994	Generic Only	2012	18
Morphine Sulfate	MS Contin	1987	Generic and Branded	2012	25
Dantrolene Sodium (capsule)	Dantrium	1974	Generic and Branded	2012	38
Estradiol	Estraderm	1986	Generic and Branded	2012	26
Lisinopril	Prinivil	1987	Generic and Branded	2012	25
Benazepril Hydrochloride	Lotensin	1991	Generic and Branded	2012	21
Trandolapril	Mavik	1996	Generic and Branded	2012	16

Generic Name	Original Brand Name	Year of Approval	Current Availability	Year of New Boxed Warning	Years from Approval to New Boxed Warning
Quinapril HCl / Hydrochlorothiazide	Accuretic	1999	Generic and Branded	2012	13
Ramipril (capsule)	Altace	1991	Generic and Branded	2012	21
Amlodipine Besylate and Benzepril Hydrochloride	Lotrel	1995	Generic and Branded	2012	17
Trandolapril / Verapamil Hyrochloride	Tarka	1996	Generic and Branded	2012	16
Eprosartan Mesylate	Teveten	1997	Generic and Branded	2012	15
Moexipril Hydrochloride	Univasc	1995	Generic and Branded	2012	17
Moexipril Hydrochloride / Hydrochlorothiazide	Uniretic	1997	Generic and Branded	2012	15
Enalapril Maleate; Hydrochlorothiazide	Vaseretic	1986	Generic and Branded	2012	26
Lisinopril and Hydrochlorothiazide	Zestoretic	1989	Generic and Branded	2012	23
Codeine	Codeine	1950	Generic and Branded (in combination products)	2013	63

Table I shows the frequency of significant safety issues identified after generics have entered the market. Over 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.[42] The data show that new safety issues commonly arise after generics have entered the market, and underscore the public health imperative of maintaining an incentive for generic manufacturer surveillance of safety concerns.

[42] Table 1 is likely incomplete because the FDA list of new warnings on which we relied to compile Table 1 did not include warnings added to two drugs—danazol and promethazine—for which new boxed warnings were required during the time period covered. *See supra* note 41.

Generic Drugs Often Lack Brand-Name Alternatives

Whether because of price competition or other reasons, it is not uncommon for the brand-name manufacturer to exit the market entirely after generic entry, leaving generic products as the only marketed versions of the drug. In that situation, the limitation on generics' ability to update labeling to provide the most current warning information takes on added significance, particularly when the drug is known to pose serious risks.

The market withdrawals of Accutane and Serzone illustrate the point.

- Isotretinoin, first marketed under the brand name Accutane, is used to treat a severe form of acne and first received FDA approval in 1982.[43] Accutane was linked to several severe side effects, including birth defects when taken by pregnant women, damage to the liver and other internal organs, and depression.[44] 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.[45] Generic versions of isotretinoin remain available.[46]

- Nefazodone hydrochloride, an antidepressant approved in 1994 as brand-name Serzone, was removed from the market by the brand-name manufacturer in 2004.[47] Although the drug had been withdrawn from the market in Canada for safety reasons[48] and is associated liver failure,[49] the company purported to stop selling it in the United States due to economic considerations.[50] Nefazodone hydrochloride remains on the market in generic form.[51]

To compile a list of prescription drugs where the brand-name manufacturer has discontinued sales but a generic equivalent remains on the market, we analyzed drugs listed in the FDA's *Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations*.[52] Sorting products in the *Orange Book*'s electronic database as of February 27, 2013, made available through the FDA's website, we identified 434 approved drugs for which no brand-name product remains on the market. These products are listed in Table 2.

[43] FDA, Drugs@FDA, Accutane, at http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm.
[44] Roche Laboratories, Inc., *Medication Guide: Accutane* 14-15 (Jan. 2010), at http://1.usa.gov/16hEwDq.
[45] Roche Pharmaceuticals, *Roche Discontinues and Plans to Delist Accutane in the U.S*. (June 29, 2009), at http://bit.ly/ZPJIvQ.
[46] FDA, Drugs@FDA, Isotretinoin, at http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm.
[47] 69 Fed. Reg. 62447, 62447 (Oct. 26, 2004), at http://1.usa.gov/17t1adG.
[48] Health Canada, *Advisory* (Nov. 10, 2003), at http://bit.ly/ZTvYOW.
[49] Public Citizen, *Petition to ban antidepressant nefazadone (Serzone)* (Mar. 6, 2003), at http://www.citizen.org/Page.aspx?pid=3299.
[50] CBS Evening News, *Anti-Depressant Taken Off Market* (Dec. 5, 2007), at http://cbsn.ws/17nn53l.
[51] FDA, Drugs@FDA, Nefazodone hydrochloride, at http://1.usa.gov/ZPJWmw.
[52] FDA, *Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations* (2013), at http://1.usa.gov/3NEz8T.

Because product safety and effectiveness varies with differing dosage levels, the FDA requires manufacturers to seek separate approval to market each dosage and dosage form of the same active ingredient, and the FDA generally lists each approved form as a separate product in the *Orange Book*. Where the FDA has separately listed different dosages and dosage forms, Table 2 does so as well.

Table 2: Generic Drugs with Unique Ingredients, Dosage Form and Route, and Strength (Brand-name product discontinued)

INGREDIENT	DOSAGE FORM & ROUTE	STRENGTH
Acetaminophen; Butalbital	Capsule; Oral	650MG; 50MG
Acetaminophen; Butalbital	Tablet; Oral	300MG; 50MG
Acetaminophen; Butalbital	Tablet; Oral	325MG; 50MG
Acetaminophen; Butalbital	Tablet; Oral	650MG; 50MG
Acetaminophen; Butalbital; Caffeine	Capsule; Oral	300MG; 50MG; 40MG
Acetaminophen; Butalbital; Caffeine	Capsule; Oral	325MG; 50MG; 40MG
Acetaminophen; Butalbital; Caffeine	Capsule; Oral	500MG; 50MG; 40MG
Acetaminophen; Butalbital; Caffeine	Solution; Oral	325MG/15ML; 50MG/15ML; 40MG/15ML
Acetaminophen; Butalbital; Caffeine	Tablet; Oral	325MG; 50MG; 40MG
Acetaminophen; Butalbital; Caffeine	Tablet; Oral	500MG; 50MG; 40MG
Acetaminophen; Butalbital; Caffeine	Tablet; Oral	750MG; 50MG; 40MG
Acetaminophen; Butalbital; Caffeine; Codeine Phosphate	Capsule; Oral	300MG; 50MG; 40MG; 30MG
Acetaminophen; Caffeine; Dihydrocodeine Bitartrate	Capsule; Oral	356.4MG; 30MG; 16MG
Acetaminophen; Caffeine; Dihydrocodeine Bitartrate	Tablet; Oral	712.8MG; 60MG; 32MG
Acetaminophen; Codeine Phosphate	Solution; Oral	120MG/5ML; 12MG/5ML
Acetaminophen; Codeine Phosphate	Suspension; Oral	120MG/5ML; 12MG/5ML
Acetaminophen; Codeine Phosphate	Tablet; Oral	300MG; 15MG
Acetaminophen; Codeine Phosphate	Tablet; Oral	300MG; 30MG
Acetaminophen; Codeine Phosphate	Tablet; Oral	300MG; 60MG
Acetaminophen; Codeine Phosphate	Tablet; Oral	650MG; 30MG
Acetaminophen; Codeine Phosphate	Tablet; Oral	650MG; 60MG
Acetaminophen; Hydrocodone Bitartrate	Capsule; Oral	500MG; 5MG
Acetaminophen; Hydrocodone Bitartrate	Solution; Oral	300MG/15ML; 10MG/15ML
Acetaminophen; Hydrocodone Bitartrate	Solution; Oral	325MG/15ML; 10MG/15ML
Acetaminophen; Hydrocodone Bitartrate	Solution; Oral	325MG/15ML; 7.5MG/15ML
Acetaminophen; Hydrocodone Bitartrate	Solution; Oral	500MG/15ML; 7.5MG/15ML
Acetaminophen; Hydrocodone Bitartrate	Tablet; Oral	300MG; 10MG
Acetaminophen; Hydrocodone Bitartrate	Tablet; Oral	300MG; 5MG
Acetaminophen; Hydrocodone Bitartrate	Tablet; Oral	300MG; 7.5MG
Acetaminophen; Hydrocodone Bitartrate	Tablet; Oral	325MG; 10MG

INGREDIENT	DOSAGE FORM & ROUTE	STRENGTH
Acetaminophen; Hydrocodone Bitartrate	Tablet; Oral	325MG; 2.5MG
Acetaminophen; Hydrocodone Bitartrate	Tablet; Oral	325MG; 5MG
Acetaminophen; Hydrocodone Bitartrate	Tablet; Oral	325MG; 7.5MG
Acetaminophen; Hydrocodone Bitartrate	Tablet; Oral	400MG; 10MG
Acetaminophen; Hydrocodone Bitartrate	Tablet; Oral	400MG; 5MG
Acetaminophen; Hydrocodone Bitartrate	Tablet; Oral	400MG; 7.5MG
Acetaminophen; Hydrocodone Bitartrate	Tablet; Oral	500MG; 10MG
Acetaminophen; Hydrocodone Bitartrate	Tablet; Oral	500MG; 2.5MG
Acetaminophen; Hydrocodone Bitartrate	Tablet; Oral	500MG; 5MG
Acetaminophen; Hydrocodone Bitartrate	Tablet; Oral	500MG; 7.5MG
Acetaminophen; Hydrocodone Bitartrate	Tablet; Oral	650MG; 10MG
Acetaminophen; Hydrocodone Bitartrate	Tablet; Oral	650MG; 5MG
Acetaminophen; Hydrocodone Bitartrate	Tablet; Oral	650MG; 7.5MG
Acetaminophen; Hydrocodone Bitartrate	Tablet; Oral	660MG; 10MG
Acetaminophen; Hydrocodone Bitartrate	Tablet; Oral	750MG; 10MG
Acetaminophen; Hydrocodone Bitartrate	Tablet; Oral	750MG; 7.5MG
Acetaminophen; Oxycodone Hydrochloride	Capsule; Oral	500MG; 5MG
Acetaminophen; Oxycodone Hydrochloride	Solution; Oral	325MG/5ML; 5MG/5ML
Acetaminophen; Oxycodone Hydrochloride	Tablet; Oral	300MG; 10MG
Acetaminophen; Oxycodone Hydrochloride	Tablet; Oral	300MG; 2.5MG
Acetaminophen; Oxycodone Hydrochloride	Tablet; Oral	300MG; 5MG
Acetaminophen; Oxycodone Hydrochloride	Tablet; Oral	300MG; 7.5MG
Acetaminophen; Oxycodone Hydrochloride	Tablet; Oral	325MG; 10MG
Acetaminophen; Oxycodone Hydrochloride	Tablet; Oral	325MG; 2.5MG
Acetaminophen; Oxycodone Hydrochloride	Tablet; Oral	325MG; 5MG
Acetaminophen; Oxycodone Hydrochloride	Tablet; Oral	325MG; 7.5MG
Acetaminophen; Oxycodone Hydrochloride	Tablet; Oral	400MG; 10MG
Acetaminophen; Oxycodone Hydrochloride	Tablet; Oral	400MG; 2.5MG
Acetaminophen; Oxycodone Hydrochloride	Tablet; Oral	400MG; 5MG
Acetaminophen; Oxycodone Hydrochloride	Tablet; Oral	400MG; 7.5MG
Acetaminophen; Oxycodone Hydrochloride	Tablet; Oral	500MG; 10MG
Acetaminophen; Oxycodone Hydrochloride	Tablet; Oral	500MG; 5MG
Acetaminophen; Oxycodone Hydrochloride	Tablet; Oral	500MG; 7.5MG
Acetaminophen; Oxycodone Hydrochloride	Tablet; Oral	650MG; 10MG
Acetic Acid, Glacial; Aluminum Acetate	Solution/Drops; Otic	2%; 0.79%
Acyclovir Sodium	Injectable; Injection	EQ 50MG base/ML
Alprazolam	Concentrate; Oral	1MG/ML
Amino Acids	Injectable; Injection	15% (150GM/1000ML)
Amino Acids	Injectable; Injection	15% (300GM/2000ML)
Aminophylline	Injectable; Injection	25MG/ML
Aminosalicylic Acid	Granule, Delayed Release; Oral	4GM/packet

INGREDIENT	DOSAGE FORM & ROUTE	STRENGTH
Amiodarone Hydrochloride	Tablet; Oral	100MG
Amiodarone Hydrochloride	Tablet; Oral	300MG
Amiodarone Hydrochloride	Tablet; Oral	400MG
Amlodipine; Hydrochlorothiazide; Valsartan	Tablet; Oral	10MG; 12.5MG; 160MG
Amlodipine; Hydrochlorothiazide; Valsartan	Tablet; Oral	10MG; 25MG; 160MG
Amlodipine; Hydrochlorothiazide; Valsartan	Tablet; Oral	10MG; 25MG; 320MG
Amlodipine; Hydrochlorothiazide; Valsartan	Tablet; Oral	5MG; 12.5MG; 160MG
Amlodipine; Hydrochlorothiazide; Valsartan	Tablet; Oral	5MG; 25MG; 160MG
Ammonia N-13	Injectable; Intravenous	3.75-260mCi/ML
Ammonium Chloride	Injectable; Injection	5MEQ/ML
Amoxicillin; Clavulanate Potassium	Suspension; Oral	200MG/5ML; EQ 28.5MG base/5ML
Amoxicillin; Clavulanate Potassium	Suspension; Oral	400MG/5ML; EQ 57MG base/5ML
Amoxicillin; Clavulanate Potassium	Suspension; Oral	600MG/5ML; EQ 42.9MG base/5ML
Amphetamine Sulfate	Tablet; Oral	10MG
Amphetamine Sulfate	Tablet; Oral	5MG
Amphotericin B	Injectable; Injection	50MG/vial
Ampicillin Sodium	Injectable; Injection	EQ 10GM base/vial
Azathioprine	Tablet; Oral	100MG
Azathioprine	Tablet; Oral	75MG
Bacitracin	Injectable; Injection	10,000 units/vial
Bacitracin	Injectable; Injection	50,000 units/vial
Bacitracin	Ointment; Ophthalmic	500 units/GM
Bacitracin	Powder; For Rx Compounding	5,000,000 units/bot
Bacitracin Zinc; Polymyxin B Sulfate	Ointment; Ophthalmic	500 units/GM; 10,000 units/GM
Bacitracin; Hydrocortisone Acetate; Neomycin Sulfate; Polymyxin B Sulfate	Ointment; Ophthalmic	400 units/GM; 1%; EQ 3.5MG base/GM; 10,000 units/GM
Benzonatate	Capsule; Oral	150MG
Bupivacaine Hydrochloride; Epinephrine	Injectable; Injection	0.25%; 0.005MG/ML
Bupivacaine Hydrochloride; Epinephrine	Injectable; Injection	0.5%; 0.005MG/ML
Buspirone Hydrochloride	Tablet; Oral	7.5MG
Butabarbital Sodium	Elixir; Oral	30MG/5ML
Carbamazepine	Tablet, Chewable; Oral	200MG
Carbamazepine	Tablet; Oral	100MG
Carbamazepine	Tablet; Oral	300MG
Carbamazepine	Tablet; Oral	400MG
Carbidopa; Levodopa	Tablet, Orally Disintegrating; Oral	10MG; 100MG
Carbidopa; Levodopa	Tablet, Orally Disintegrating; Oral	25MG; 100MG
Carbidopa; Levodopa	Tablet, Orally Disintegrating; Oral	25MG; 250MG

INGREDIENT	DOSAGE FORM & ROUTE	STRENGTH
Carbinoxamine Maleate	Solution; Oral	4MG/5ML
Carboplatin	Injectable; Iv (Infusion)	1GM/100ML (10MG/ML)
Cefaclor	For Suspension; Oral	EQ 187MG base/5ML
Cefaclor	For Suspension; Oral	EQ 375MG base/5ML
Cefazolin Sodium	Injectable; Injection	EQ 100GM base/VIAL
Cefazolin Sodium	Injectable; Injection	EQ 20GM base/VIAL
Cefazolin Sodium	Injectable; Injection	EQ 300GM base/VIAL
Cefixime	Suspension; Oral	100MG/5ML
Cefixime	Suspension; Oral	200MG/5ML
Cefixime	Tablet, Chewable; Oral	100MG
Cefixime	Tablet, Chewable; Oral	150MG
Cefixime	Tablet, Chewable; Oral	200MG
Ceftriaxone Sodium	Injectable; Injection	EQ 500MG base/vial
Cefuroxime Sodium	Injectable; Injection	EQ 225GM base/vial
Cefuroxime Sodium	Injectable; Injection	EQ 75GM base/vial
Chloroquine Phosphate	Tablet; Oral	EQ 150MG base
Chlorpheniramine Polistirex; Hydrocodone Polistirex	Capsule, Extended Release; Oral	EQ 4MG Maleate; EQ 5MG Bitartrate
Chlorpheniramine Polistirex; Hydrocodone Polistirex	Capsule, Extended Release; Oral	EQ 8MG Maleate; EQ 10MG Bitartrate
Chlorzoxazone	Tablet; Oral	375MG
Chlorzoxazone	Tablet; Oral	750MG
Citalopram Hydrobromide	Capsule; Oral	EQ 10MG base
Citalopram Hydrobromide	Capsule; Oral	EQ 20MG base
Citalopram Hydrobromide	Capsule; Oral	EQ 40MG base
Clindamycin Palmitate Hydrochloride	For Solution; Oral	EQ 75MG base/5ML
Clonidine Hydrochloride	Injectable; Injection	1MG/10ML (0.1MG/ML)
Clonidine Hydrochloride	Injectable; Injection	5MG/10ML (0.5MG/ML)
Clozapine	Tablet; Oral	12.5MG
Clozapine	Tablet; Oral	200MG
Clozapine	Tablet; Oral	50MG
Cyclobenzaprine Hydrochloride	Tablet; Oral	7.5MG
Cyclopentolate Hydrochloride	Solution/Drops; Ophthalmic	0.5%
Cyclopentolate Hydrochloride	Solution/Drops; Ophthalmic	1%
Cyclopentolate Hydrochloride	Solution/Drops; Ophthalmic	2%
Cyclopentolate Hydrochloride; Phenylephrine Hydrochloride	Solution/Drops; Ophthalmic	0.2%; 1%
Cycloserine	Capsule; Oral	250MG
Cytarabine	Injectable; Injection	100MG/ML
Cytarabine	Injectable; Injection	20MG/ML
Dacarbazine	Injectable; Injection	500MG/vial
Dapsone	Tablet; Oral	100MG
Dapsone	Tablet; Oral	25MG

INGREDIENT	DOSAGE FORM & ROUTE	STRENGTH
Daunorubicin Hydrochloride	Injectable; Injection	EQ 5MG base/vial
Desonide	Lotion; Topical	0.05%
Dexamethasone	Concentrate; Oral	1MG/ML
Dexamethasone	Solution; Oral	0.5MG/5ML
Dexamethasone	Tablet; Oral	1MG
Dexamethasone	Tablet; Oral	2MG
Dexchlorpheniramine Maleate	Syrup; Oral	2MG/5ML
Dextroamphetamine Sulfate	Solution; Oral	5MG/5ML
Dextroamphetamine Sulfate	Tablet; Oral	10MG
Dextroamphetamine Sulfate	Tablet; Oral	15MG
Dextroamphetamine Sulfate	Tablet; Oral	2.5MG
Dextroamphetamine Sulfate	Tablet; Oral	20MG
Dextroamphetamine Sulfate	Tablet; Oral	30MG
Dextroamphetamine Sulfate	Tablet; Oral	5MG
Dextroamphetamine Sulfate	Tablet; Oral	7.5MG
Diazepam	Concentrate; Oral	5MG/ML
Diazepam	Solution; Oral	5MG/5ML
Dicloxacillin Sodium	Capsule; Oral	EQ 125MG base
Diltiazem Hydrochloride	Injectable; Injection	10MG/ML
Dimenhydrinate	Injectable; Injection	50MG/ML
Doxycycline	Capsule; Oral	EQ 150MG base
Doxycycline	Tablet; Oral	EQ 100MG base
Doxycycline	Tablet; Oral	EQ 150MG base
Doxycycline	Tablet; Oral	EQ 50MG base
Doxycycline	Tablet; Oral	EQ 75MG base
Epinephrine Bitartrate; Lidocaine Hydrochloride	Injectable; Injection	EQ 0.01MG base/ML; 2%
Epinephrine Bitartrate; Lidocaine Hydrochloride	Injectable; Injection	EQ 0.02MG base/ML; 2%
Epirubicin Hydrochloride	Injectable; Injection	10MG/5ML (2MG/ML)
Epirubicin Hydrochloride	Injectable; Injection	150MG/75ML (2MG/ML)
Ergotamine Tartrate	Tablet; Sublingual	2MG
Erythromycin	Tablet, Delayed Release; Oral	250MG
Erythromycin	Tablet, Delayed Release; Oral	333MG
Erythromycin	Tablet, Delayed Release; Oral	500MG
Erythromycin	Tablet; Oral	250MG
Erythromycin	Tablet; Oral	500MG
Erythromycin Ethylsuccinate	Suspension; Oral	EQ 200MG base/5ML
Erythromycin Ethylsuccinate	Suspension; Oral	EQ 400MG base/5ML
Erythromycin Ethylsuccinate	Tablet; Oral	EQ 400MG base
Erythromycin Stearate	Tablet; Oral	EQ 250MG base
Estradiol	Cream; Vaginal	0.01%
Estradiol	Tablet; Oral	0.5MG

INGREDIENT	DOSAGE FORM & ROUTE	STRENGTH
Estradiol	Tablet; Oral	1MG
Estradiol	Tablet; Oral	2MG
Estradiol Cypionate	Injectable; Injection	5MG/ML
Estrogens, Esterified	Tablet; Oral	0.3MG
Estrogens, Esterified	Tablet; Oral	0.625MG
Estrogens, Esterified	Tablet; Oral	1.25MG
Estrogens, Esterified	Tablet; Oral	2.5MG
Estropipate	Tablet; Oral	0.75MG
Estropipate	Tablet; Oral	1.5MG
Estropipate	Tablet; Oral	3MG
Estropipate	Tablet; Oral	6MG
Ethinyl Estradiol; Norgestimate	Tablet; Oral	0.035MG; 0.035MG; 0.035MG; 0.18MG; 0.215MG; 0.25MG
Ethosuximide	Syrup; Oral	250MG/5ML
Famotidine	Suspension; Oral	40MG/5ML
Fenofibrate	Tablet; Oral	107MG
Fluconazole	Injectable; Injection	100MG/50ML (2MG/ML)
Fludeoxyglucose F-18	Injectable; Intravenous	20-500mCi/ML
Fluorouracil	Injectable; Injection	1GM/20ML (50MG/ML)
Fluorouracil	Injectable; Injection	2.5GM/50ML (50MG/ML)
Fluorouracil	Injectable; Injection	5GM/100ML (50MG/ML)
Fosinopril; Hydrochlorothiazide	Tablet; Oral	10MG; 12.5MG
Fosinopril; Hydrochlorothiazide	Tablet; Oral	20MG; 12.5MG
Fosphenytoin Sodium	Injectable; Injection	EQ 50MG pnenytoin NA/ML
Furosemide	Solution; Oral	40MG/5ML
Gabapentin	Tablet; Oral	100MG
Gabapentin	Tablet; Oral	400MG
Gemcitabine Hydrochloride	Injectable; Injection	EQ 2GM base/vial
Gentamicin Sulfate	Cream; Topical	EQ 0.1% base
Gentamicin Sulfate	Injectable; Injection	EQ 0.8MG base/ML
Gentamicin Sulfate	Injectable; Injection	EQ 1.2MG base/ML
Gentamicin Sulfate	Injectable; Injection	EQ 1.4MG base/ML
Gentamicin Sulfate	Injectable; Injection	EQ 1.6MG base/ML
Gentamicin Sulfate	Injectable; Injection	EQ 1.8MG base/ML
Gentamicin Sulfate	Injectable; Injection	EQ 100MG base/100ML
Gentamicin Sulfate	Injectable; Injection	EQ 10MG base/ML
Gentamicin Sulfate	Injectable; Injection	EQ 120MG base/100ML
Gentamicin Sulfate	Injectable; Injection	EQ 2.4MG base/ML
Gentamicin Sulfate	Injectable; Injection	EQ 2MG base/ML
Gentamicin Sulfate	Injectable; Injection	EQ 40MG base/100ML
Gentamicin Sulfate	Injectable; Injection	EQ 40MG base/ML

INGREDIENT	DOSAGE FORM & ROUTE	STRENGTH
Gentamicin Sulfate	Injectable; Injection	EQ 60MG base/100ML
Gentamicin Sulfate	Injectable; Injection	EQ 70MG base/100ML
Gentamicin Sulfate	Injectable; Injection	EQ 80MG base/100ML
Gentamicin Sulfate	Injectable; Injection	EQ 90MG base/100ML
Gentamicin Sulfate	Ointment; Topical	EQ 0.1% base
Glimepiride	Tablet; Oral	3MG
Glimepiride	Tablet; Oral	6MG
Glimepiride	Tablet; Oral	8MG
Glycopyrrolate	Tablet; Oral	1.5MG
Gramicidin; Neomycin Sulfate; Polymyxin B Sulfate	Solution/Drops; Ophthalmic	0.025MG/ML; EQ 1.75MG base/ML; 10,000 units/ML
Griseofulvin, Microsize	Suspension; Oral	125MG/5ML
Griseofulvin, Microsize	Tablet; Oral	500MG
Hydralazine Hydrochloride; Hydrochlorothiazide	Capsule; Oral	25MG; 25MG
Hydralazine Hydrochloride; Hydrochlorothiazide	Capsule; Oral	50MG; 50MG
Hydrochlorothiazide	Tablet; Oral	12.5MG
Hydrochlorothiazide; Quinapril Hydrochloride	Tablet; Oral	12.5MG; 10MG
Hydrochlorothiazide; Quinapril Hydrochloride	Tablet; Oral	12.5MG; 20MG
Hydrochlorothiazide; Quinapril Hydrochloride	Tablet; Oral	25MG; 20MG
Hydrocodone Bitartrate; Ibuprofen	Tablet; Oral	10MG; 200MG
Hydrocodone Bitartrate; Ibuprofen	Tablet; Oral	2.5MG; 200MG
Hydrocodone Bitartrate; Ibuprofen	Tablet; Oral	5MG; 200MG
Hydrocortisone	Cream; Topical	2.5%
Hydrocortisone	Lotion; Topical	2%
Hydrocortisone	Lotion; Topical	2.5%
Hydrocortisone	Powder; For Rx Compounding	100%
Hydrocortisone	Solution; Topical	2.5%
Hydrocortisone Acetate	Cream; Topical	2%
Hydrocortisone Acetate	Cream; Topical	2.5%
Hydrocortisone Acetate	Paste; Topical	0.5%
Hydrocortisone Acetate	Powder; For Rx Compounding	100%
Hydrocortisone Acetate; Pramoxine Hydrochloride	Aerosol, Metered; Topical	1%; 1%
Hydrocortisone Acetate; Pramoxine Hydrochloride	Cream; Topical	0.5%; 1%
Hydrocortisone Acetate; Pramoxine Hydrochloride	Cream; Topical	1%; 1%
Hydrocortisone Acetate; Pramoxine Hydrochloride	Lotion; Topical	1%; 1%
Hydrocortisone Acetate; Pramoxine Hydrochloride	Lotion; Topical	2.5%; 1%
Hydrocortisone Acetate; Urea	Cream; Topical	1%; 10%
Hydrocortisone; Neomycin Sulfate; Polymyxin B Sulfate	Suspension/Drops; Otic	1%; EQ 3.5MG base/ML; 10,000 units/ML
Hydroxocobalamin	Injectable; Injection	1MG/ML
Ifosfamide	Injectable; Injection	1GM/20ML (50MG/ML)
Ifosfamide	Injectable; Injection	1GM/20ML (50MG/ML)

INGREDIENT	DOSAGE FORM & ROUTE	STRENGTH
Ifosfamide	Injectable; Injection	3GM/60ML (50MG/ML)
Ifosfamide	Injectable; Injection	3GM/60ML (50MG/ML)
Ifosfamide; Mesna	Injectable; Intravenous	1GM/20ML; 1GM/10ML (50MG/ML; 100MG/ML)
Ifosfamide; Mesna	Injectable; Intravenous	3GM/60ML; 1GM/10ML (50MG/ML; 100MG/ML)
Irinotecan Hydrochloride	Injectable; Injection	500MG/25ML (20MG/ML)
Isoniazid; Rifampin	Capsule; Oral	150MG; 300MG
Kanamycin Sulfate	Injectable; Injection	EQ 1GM base/3ML
Kanamycin Sulfate	Injectable; Injection	EQ 500MG base/2ML
Lactulose	For Solution; Oral	10GM/packet
Lactulose	For Solution; Oral	20GM/packet
Leucovorin Calcium	Injectable; Injection	EQ 10MG base/ML
Leucovorin Calcium	Injectable; Injection	EQ 200MG base/vial
Leucovorin Calcium	Injectable; Injection	EQ 500MG base/vial
Leucovorin Calcium	Tablet; Oral	EQ 10MG base
Leucovorin Calcium	Tablet; Oral	EQ 15MG base
Levetiracetam	Injectable; IV (Infusion)	500MG/5ML(100MG/ML)
Levetiracetam	Injectable; IV (Infusion)	500MG/ML (100MG/ML)
Levofloxacin	Injectable; Injection	EQ 500MG/100ML (EQ5MG/ML)
Lorazepam	Concentrate; Oral	2MG/ML
Meperidine Hydrochloride	Injectable; Injection	10MG/ML
Meperidine Hydrochloride	Tablet; Oral	150MG
Meperidine Hydrochloride	Tablet; Oral	75MG
Methadone Hydrochloride	Solution; Oral	10MG/5ML
Methadone Hydrochloride	Solution; Oral	5MG/5ML
Methotrexate Sodium	Injectable; Injection	EQ 100MG base/4ML (EQ 25MG base/ML)
Methotrexate Sodium	Injectable; Injection	EQ 200MG base/8ML (EQ 25MG base/ML)
Methotrexate Sodium	Injectable; Injection	EQ 250MG base/10ML (EQ 25MG base/ML)
Methotrexate Sodium	Injectable; Injection	EQ 250MG/10ML (EQ 25MG base/ML)
Methotrexate Sodium	Tablet; Oral	EQ 10MG base
Methotrexate Sodium	Tablet; Oral	EQ 15MG base
Methotrexate Sodium	Tablet; Oral	EQ 5MG base
Methotrexate Sodium	Tablet; Oral	EQ 7.5MG base
Methylphenidate Hydrochloride	Tablet, Extended Release; Oral	10MG
Methyltestosterone	Capsule; Oral	10MG
Metoprolol Succinate	Tablet, Extended Release; Oral	EQ 100MG base
Metoprolol Succinate	Tablet, Extended Release; Oral	EQ 200MG base

INGREDIENT	DOSAGE FORM & ROUTE	STRENGTH
Metoprolol Tartrate	Tablet; Oral	25MG
Minocycline Hydrochloride	Tablet; Oral	EQ 75MG base
Mirtazapine	Tablet; Oral	7.5MG
Mitomycin	Injectable; Injection	40MG/vial
Mitoxantrone	Injectable; Injection	EQ 20MG base/10ML (EQ 2MG base/ML)
Nafcillin Sodium	Injectable; Injection	EQ 1GM base
Nafcillin Sodium	Injectable; Injection	EQ 2GM base
Naltrexone Hydrochloride	Tablet; Oral	100MG
Naltrexone Hydrochloride	Tablet; Oral	25MG
Naphazoline Hydrochloride	Solution/Drops; Ophthalmic	0.1%
Naratriptan	Tablet; Oral	EQ 1MG base
Naratriptan	Tablet; Oral	EQ 2.5MG base
Neomycin Sulfate	Powder; For Rx Compounding	100%
Neomycin Sulfate	Tablet; Oral	500MG
Neomycin Sulfate; Polymyxin B Sulfate	Solution; Irrigation	EQ 40MG base/ML; 200,000 units/ML
Niacin	Tablet; Oral	500MG
Nitroglycerin	Ointment; Transdermal	2%
Nystatin	Cream; Topical	100,000 units/GM
Nystatin	Ointment; Topical	100,000 units/GM
Nystatin	Powder; Topical	100,000 units/GM
Nystatin	Tablet; Oral	500,000 units
Nystatin	Tablet; Vaginal	100,000 units
Nystatin; Triamcinolone Acetonide	Cream; Topical	100,000 units/GM; 0.1%
Nystatin; Triamcinolone Acetonide	Ointment; Topical	100,000 units/GM; 0.1%
Ondansetron Hydrochloride	Tablet; Oral	EQ 16MG base
Oxacillin Sodium	Injectable; Injection	EQ 10GM base/vial
Oxaliplatin	Injectable; IV (infusion)	50MG/vial
Oxtriphylline	Tablet, Extended Release; Oral	400MG
Oxtriphylline	Tablet, Extended Release; Oral	600MG
Oxycodone Hydrochloride	Tablet; Oral	10MG
Oxycodone Hydrochloride	Tablet; Oral	20MG
Oxytetracycline Hydrochloride; Polymyxin B Sulfate	Ointment; Ophthalmic	EQ 5MG base/GM; 10,000 units/GM
Pamidronate Disodium	Injectable; Injection	60MG/10ML (6MG/ML)
Paromomycin Sulfate	Capsule; Oral	EQ 250MG base
Penicillin G Potassium	Injectable; Injection	1,000,000 units/vial
Penicillin G Potassium	Injectable; Injection	20,000,000 units/vial
Penicillin G Potassium	Injectable; Injection	5,000,000 units/vial
Penicillin G Procaine	Injectable; Injection	300,000 units/ML
Penicillin G Procaine	Injectable; Injection	600,000 units/ML

INGREDIENT	DOSAGE FORM & ROUTE	STRENGTH
Penicillin G Sodium	Injectable; IM-IV	5,000,000 units/vial
Penicillin V Potassium	For Solution; Oral	EQ 125MG base/5ML
Penicillin V Potassium	For Solution; Oral	EQ 250MG base/5ML
Penicillin V Potassium	Tablet; Oral	EQ 250MG base
Penicillin V Potassium	Tablet; Oral	EQ 500MG base
Pentobarbital Sodium	Injectable; Injection	50MG/ML
Phentermine Hydrochloride	Capsule; Oral	15MG
Phentermine Hydrochloride	Capsule; Oral	37.5MG
Phentermine Hydrochloride	Tablet; Oral	37.5MG
Phenylephrine Hydrochloride; Promethazine Hydrochloride	Syrup; Oral	5MG/5ML; 6.25MG/5ML
Phenytoin	Tablet, Chewable; Oral	50MG
Phenytoin Sodium	Capsule; Oral	100MG extended
Phenytoin Sodium	Capsule; Oral	200MG extended
Phenytoin Sodium	Capsule; Oral	300MG extended
Phenytoin Sodium	Capsule; Oral	30MG extended
Polyethylene Glycol 3350; Potassium Chloride; Sodium Bicarbonate; Sodium Chloride; Sodium Sulfate Anhydrous	For Solution; Oral	236GM; 2.97GM; 6.74GM; 5.86GM; 22.74GM
Polymyxin B Sulfate	Injectable; Injection	EQ 500,000 units base/vial
Polymyxin B Sulfate	Injectable; Injection	EQ 500,000 units base/vial
Polymyxin B Sulfate	Powder; For Rx Compounding	100,000,000 units/bot
Potassium Chloride	Injectable; Injection	3MEQ/ML
Potassium Chloride	Tablet, Extended Release; Oral	15MEQ
Potassium Chloride; Sodium Chloride	Injectable; Injection	149MG/100ML; 450MG/100ML
Prednisolone	Syrup; Oral	15MG/5ML
Prednisolone	Syrup; Oral	5MG/5ML
Prednisolone Acetate; Sulfacetamide Sodium	Ointment; Ophthalmic	0.2%; 10%
Prednisolone Sodium Phosphate	Solution/Drops; Ophthalmic	EQ 0.9% phosphate
Prednisolone Sodium Phosphate	Solution; Oral	EQ 10MG base/5ML
Prednisolone Sodium Phosphate	Solution; Oral	EQ 15MG base /5ML
Prednisolone Sodium Phosphate	Solution; Oral	EQ 20MG base /5ML
Prednisolone Sodium Phosphate	Solution; Oral	EQ 25MG base /5ML
Prednisone	Solution; Oral	5MG/5ML
Prednisone	Solution; Oral	5MG/ML
Propranolol Hydrochloride	Solution; Oral	20MG/5ML
Propranolol Hydrochloride	Solution; Oral	40MG/5ML
Pyrazinamide	Tablet; Oral	500MG
Pyridoxine Hydrochloride	Injectable; Injection	100MG/ML
Quinidine Sulfate	Tablet; Oral	200MG
Quinidine Sulfate	Tablet; Oral	300MG

INGREDIENT	DOSAGE FORM & ROUTE	STRENGTH
Ribavirin	Tablet; Oral	500MG
Ribavirin	Tablet; Oral	600MG
Rifampin	Capsule; Oral	150MG
Risperidone	Tablet, Orally Disintegrating; Oral	0.25MG
Secobarbital Sodium	Capsule; Oral	100MG
Secobarbital Sodium	Capsule; Oral	50MG
Sodium Nitroprusside	Injectable; Injection	25MG/ML
Sodium Polystyrene Sulfonate	Powder; Oral; Rectal	454GM/bot
Sodium Polystyrene Sulfonate	Suspension; Oral; Rectal	15GM/60ML
Sodium Tetradecyl Sulfate	Injectable; Injection	20MG/2ML (10MG/ML)
Sodium Tetradecyl Sulfate	Injectable; Injection	60MG/2ML (30MG/ML)
Streptomycin Sulfate	Injectable; Injection	EQ 1GM base/vial
Technetium Tc-99m Sestamibi Kit	Injectable; Injection	10-30mCi
Testosterone	Pellet; Implantation	75MG
Testosterone Cypionate	Injectable; Injection	100MG/ML
Testosterone Cypionate	Injectable; Injection	200MG/ML
Tetracycline Hydrochloride	Capsule; Oral	100MG
Tetrahydrozoline Hydrochloride	Solution; Nasal	0.05%
Tetrahydrozoline Hydrochloride	Solution; Nasal	0.1%
Tetrahydrozoline Hydrochloride	Spray; Nasal	0.1%
Theophylline	Capsule, Extended Release; Oral	100MG
Theophylline	Capsule, Extended Release; Oral	200MG
Theophylline	Capsule, Extended Release; Oral	300MG
Theophylline	Capsule, Extended Release; Oral	400MG
Theophylline	Elixir; Oral	80MG/15ML
Theophylline	Solution; Oral	80MG/15ML
Theophylline	Tablet, Extended Release; Oral	100MG
Theophylline	Tablet, Extended Release; Oral	200MG
Theophylline	Tablet, Extended Release; Oral	300MG
Theophylline	Tablet, Extended Release; Oral	400MG
Theophylline	Tablet, Extended Release; Oral	450MG
Theophylline	Tablet, Extended Release; Oral	600MG
Theophylline	Tablet; Oral	125MG
Theophylline	Tablet; Oral	250MG
Thiamine Hydrochloride	Injectable; Injection	100MG/ML
Thiamine Hydrochloride	Injectable; Injection	200MG/ML

INGREDIENT	DOSAGE FORM & ROUTE	STRENGTH
Tobramycin Sulfate	Injectable; Injection	EQ 1.2MG base/ML
Tobramycin Sulfate	Injectable; Injection	EQ 1.6MG base/ML
Tobramycin Sulfate	Injectable; Injection	EQ 40MG base/ML
Tobramycin Sulfate	Injectable; Injection	EQ 80MG base/100ML
Tretinoin	Cream; Topical	0.0375%
Tretinoin	Cream; Topical	0.075%
Triamcinolone Acetonide	Cream; Topical	0.5%
Triamcinolone Acetonide	Ointment; Topical	0.05%
Triamcinolone Acetonide	Ointment; Topical	0.5%
Vancomycin Hydrochloride	Injectable; Injection	EQ 10GM base/vial
Vancomycin Hydrochloride	Injectable; Injection	EQ 1GM base/vial
Vancomycin Hydrochloride	Injectable; Injection	EQ 500MG base/vial
Vancomycin Hydrochloride	Injectable; Injection	EQ 5GM base/vial
Vancomycin Hydrochloride	Injectable; Injection	EQ 750MG base/vial
Vinblastine Sulfate	Injectable; Injection	1MG/ML
Vinorelbine	Injectable; Injection	EQ 10MG base/ML

Source: Public Citizen Analysis of FDA *Orange Book*.

Regulatory Regime Creates Safety and Accountability Gap

As evidenced by Table 1, new serious risks to patients are sometimes identified years after a drug enters the market, making a drug's longevity no guarantee of safety. As Table 2 illustrates, hundreds of generic drugs are sold without a currently marketed brand-name equivalent. These facts make generic drug manufacturers' inability under current regulations to update the labeling of their products a threat to the safety of prescription drugs, and, accordingly, a source of unnecessary risks to patients.

First, as explained above, generic drugs gain a large market share for a particular drug soon after they enter the market, thereby making prescription drugs more affordable. Yet while the market shares of generic drugs have increased, the regulatory system has not adjusted to compel generic manufacturers to shoulder responsibility commensurate with their status as major market players. At the same time, the dominance of generics weakens the incentive for brand-name manufacturers to remain actively engaged in the market for their products after generics come on the market.

Under the laws 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.[53] When more than 75 percent of all prescriptions are filled by generic versions, this legal

[53] Jim Beck & Mark Hermann, *Scorecard: Innovator Liability In Generic Drug Cases*, Drug and Device Law Blog (Nov. 12, 2009), at http://druganddevicelaw.blogspot.com/2009/11/scorecard-non-manufacturer-name-brand.html.

reality further diminishes the name-brand manufacturer's incentive to be vigilant and to take the time and expense to submit a CBE or PAS.

These developments collectively give rise to a safety problem: As generic market share increases, the brand-name manufacturer loses incentive to invest resources in post-approval safety monitoring, while generic manufacturers face no concomitant increase in incentive and have no authority to update labeling. Given that the FDA cannot monitor all post-approval data by itself, drug safety is threatened when the regulatory and common-law incentives designed to motivate manufacturer diligence weaken with shifting control of market share.

Drug safety would benefit if generic manufacturers who already have access to much of the relevant information were able to use CBE and PAS procedures to revise labeling. Once a manufacturer has achieved a certain market share, it should be given the tools to share responsibilities for drug safety and labeling.

Second, in *PLIVA v. Mensing*, the Supreme Court held that because FDA regulations give generic manufacturers no control over drug labeling, it would be impossible for those manufacturers to comply with both federal law and a state-law duty to provide an adequate warning, even assuming that the approved warning is inadequate. Accordingly, the Court held, state-law duties to provide adequate warnings are preempted and generic manufacturers cannot be held accountable to patients for injuries caused by their products.[54]

The dissent in *PLIVA* noted (and the majority did not disagree) that the Court's holding produces "absurd consequences."[55] First, it threatens drug safety by creating a "gap in the parallel federal-state regulatory scheme."[56] Second, 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—deviates from the "sameness" principle central to the Hatch-Waxman Amendments by distinguishing generics in a crucial respect: "Consumers of brand-name drugs can sue manufacturers for inadequate warnings; consumers of generic drugs cannot."[57] The FDA expressed similar concerns in its amicus brief to the Court, noting that generic manufacturers "argue that they enjoy a free pass accorded to virtually no other manufacturer regarding product labeling—in the field of

[54] *PLIVA v. Mensing*, 131 S. Ct. at 2577.
[55] *Id*. at 2592 (Sotomayor, J., dissenting).
[56] *Ibid*.; *see also Wyeth v. Levine,* 555 U.S. 555, 579 (2009) ("[T]he FDA long maintained that state law offers an additional, and important, layer of consumer protection that complements FDA regulation.").
[57] *PLIVA v. Mensing*, 131 S. Ct. at 2593 (Sotomayor, J., dissenting).

drugs or otherwise."[58] In addition, the outcome is in tension with generic substitution laws, as they encourage or even require that prescriptions be filled with generic drugs when possible, but patients' inability to hold generic manufacturers accountable for inadequate labeling (whether the inadequacy is specific to a hazard associated with that generic or applies to the drug more generally) provides incentive for patients to request the brand-name drug instead of the generic. This outcome is also directly contrary to the objective of the Hatch-Waxman Amendments.

State-law remedies "further consumer protection by motivating manufacturers to produce safe and effective drugs and to give adequate warnings."[59] Today, preemption of common-law claims against generic manufactures strips a vast portion of the market of these safeguards.

Conclusion

Too often, a serious safety hazard is not identified until years after a prescription drug comes on the market, and many prescription drugs today are marketed only in generic form. For these reasons, the FDA's restriction on labeling revisions by generic drug manufacturers creates a gap that threatens patient health and safety.

[58] Brief for the United States as Amicus Curiae Supporting Resp'ts 26, *PLIVA, Inc. v. Mensing*, S. Ct. Nos. 09-993, 09-1039, 09-1501 (2011), at http://bit.ly/10VniqP.

[59] *Wyeth v. Levine*, 555 U.S. at 574.