

Nos. 09-993, 09-1039, 09-1501

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**In the Supreme Court of the United States**

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PLIVA, INC., *et al.*, *Petitioners*,  
v.  
GLADYS MENSING, *Respondent*.

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ACTAVIS ELIZABETH, LLC, *Petitioner*,  
v.  
GLADYS MENSING, *Respondent*.

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ACTAVIS INC., *Petitioner*,  
v.  
JULIE DEMAHY, *Respondent*.

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On Writs of *Certiorari* to the United States Courts  
of Appeals for the Eighth and Fifth Circuits

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**BRIEF OF JEROME P. KASSIRER, M.D., AND  
PAUL D. STOLLEY, M.D., M.P.H., AS  
AMICI CURIAE FOR RESPONDENTS**

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## QUESTION PRESENTED

Does the Drug Price Competition and Patent Term Restoration Act of 1984 [“Hatch-Waxman Act”]<sup>1</sup> preempt state-law failure-to-warn claims against manufacturers of generic drugs?

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<sup>1</sup>Pub. L. No. 98-417, 98 Stat. 1585 (1984); *see* 21 U.S.C. §156 and 35 U.S.C. §271.

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## INTEREST OF *AMICI CURIAE*

*Amici Curiae* are distinguished physicians and academicians with decades of experience in public health and drug safety.

*Amicus* Jerome P. Kassirer, M.D., Distinguished Professor at Tufts University School of Medicine, served as *New England Journal of Medicine's* ["NEJM"] Editor-in-Chief between 1991 and 1999, after which he was named Editor-in-Chief Emeritus. NEJM is the oldest continuously published medical journal in the world and one of the most respected. During his tenure at NEJM, it published numerous scholarly articles on prescription drug side effects and the respective roles of the U.S. Food and Drug Administration ["FDA"] and pharmaceutical industry in the nation's health care system.

*Amicus* Paul D. Stolley, M.D., M.P.H., has spent 40 years working in the fields of epidemiology and public health with a special focus on adverse drug reactions and how to prevent them. He is a faculty member of the Johns Hopkins School of Public Health, The University of Pennsylvania School of Medicine, and Chairman of the Department of Epidemiology and Public Health at the University of Maryland School of Medicine. Dr. Stolley has served on many advisory committees, most dealing with drug safety, for FDA, National Institutes of Health ["NIH"], and the National Academy of Science's Institute of Medicine ["IOM"], where he is an elected Member. In particular, Dr. Stolley spent a sabbatical year at FDA as consultant to its Drug Safety Division. He also served as President of the Society for Epidemiologic Research and the American Epidemiologic Society. An NEJM Editorial Board member from 1989-1993, Dr. Stolley

has published over 200 articles and 30 book chapters, including 15 in NEJM, many dealing with the epidemiology of adverse drug reactions, drug regulation, and surveillance and prevention of drug reactions. He is also co-author of three books in the field of epidemiology.

The question presented to this Court – whether federal law preempts failure-to-warn claims relating to generic drugs – is one of great significance to public health and safety. It also falls directly within *amici*'s professional expertise and responsibility to ensure that prescription drugs best serve the cause of public health. To that end, *amici* are compelled to file this brief. They ask this Court to affirm the decisions below.

## SUMMARY OF ARGUMENT

The safety profile of prescription drugs – what their side effects might be and the likelihood of their occurrence – is not static. Instead, as drugs are prescribed for more and varied patients, studied by doctors and scientists, evaluated for new indications, and reevaluated for traditional ones, sometimes over decades, their safety profiles evolve. Once cheered as a “wonder drug” for morning sickness in Europe, Thalidomide was subsequently banned in the United States when it was found to cause severe birth defects. Decades later, it reemerged as a cancer treatment. The establishment of a drug's safety profile is, therefore, an ongoing, organic process, a fact FDA and NIH concede.

Equally important, this evolution often takes time. One study found that “many serious ADRs [adverse drug reactions] are discovered only after a drug has been on the market for years. Only half of newly discovered serious ADRs are detected and documented

in the Physicians' Desk Reference within 7 years after drug approval.”<sup>2</sup>

Petitioners and their industry amici, however, ask this Court to immunize them from state failure-to-warn lawsuits based on the false assumption that safety profiles of *generic* drugs are definitively established upon FDA approval. They argue that, because generic drug manufacturers need not conduct clinical trials before their drugs may be marketed in the United States, brand-name manufacturers' pre-approval studies suffice to “validate the generic product's safety...” Brief of Petitioners Pliva, Inc., *et al.*, at 11. They, therefore, ask this Court to free them from responsibility for revising or seeking revisions to their labeling, or otherwise informing doctors and patients when new or more serious side effects associated with their drugs emerge because the safety profiles of FDA-approved generic drugs are definitely established unless and until FDA alone changes them.

In *Wyeth v. Levine*, 129 S. Ct. 1187, 1210 (2009), this Court rejected the notion that safety profiles of new drugs are conclusively established when they are approved by FDA. Both FDA and NIH recognize the inherent and practical limitations of pre-approval clinical trials in assessing drug safety and the need for ongoing, post-marketing monitoring of a drug's safety over its market life.

These considerations only grow in importance when FDA approves generic equivalents. Federal law authorizes their approval when brand-name drugs' legal protections end, not because their safety profile

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<sup>2</sup>Karen Lasser, *et al.*, *Timing of New Black Box Warnings and Withdrawals for Prescription Medication*, 287 JAMA 2215, 2218 (May 1, 2002).

has been definitively established. In fact, because the time between FDA approval of a new drug and its generic equivalent is often as short as four years, it is unlikely that a drug's safety profile will have time to emerge before generics are marketed.

Instead, as the case of metoclopramide [Reglan] demonstrates, many widely-used prescription drugs have been withdrawn or had their use severely restricted when serious side effects were identified decades after FDA first approved their use. In the case of promethazine [Phenergan], its true dangers were not revealed until more than 50 years after approval and years after generic equivalents were approved.

The battle over suicide warnings for selective serotonin reuptake inhibitor ["SSRI"] antidepressants began shortly after Prozac [fluoxetine] was approved. It lasted twenty years, long after generic SSRI equivalents had flooded the market. With gabapentin [Neurontin], an anti-epilepsy drug, FDA and the medical community were misled about its suicide risks for years by its manufacturer's public denials and illegal promotion of wide-ranging, off-label use. In the mean time, generic equivalents competed for the expanded market.

Finally, the story of isotretinoin [Accutane] shows how information about devastating side effects can be hidden from the medical community, regulators, and patients for years behind inadequate warnings. These histories starkly illustrate the Herculean task FDA *already* faces in attempting to ensure the safety of prescription drugs. Petitioners would increase that burden exponentially by making FDA the sole arbiter of drug safety.

By any objective measure, FDA lacks adequate information, resources, and authority to protect the

public against pharmaceutical risks. In fact, FDA concedes that its post-marketing responsibilities have outstripped the resources and authority available to address them. In desperation, it has resorted to regulatory triage, marshaling its limited resources to address only high-risks.

This untenable situation – that will worsen if Petitioners succeed here – has not been remedied by passage of the Food and Drug Administration Amendments Act [“FDAAA”], Pub. L. 110-85, 121 Stat. 823 (2007). It does not empower FDA to act unilaterally or immediately; therefore, it does not remedy the problems three comprehensive studies identified.

Finally, while FDA’s proposed data-mining programs might assist it in post-marketing monitoring some day, technical and financial limitations, privacy, and constitutional concerns cast doubt on FDA’s ability to implement them in the foreseeable future.

For these and the reasons that follow, the decisions of the courts below should be affirmed.

## ARGUMENT

### **I. A PRESCRIPTION DRUG’S SAFETY PROFILE IS NOT DEFINITELY ESTABLISHED BECAUSE FDA APPROVES ITS MARKETING IN GENERIC FORM**

In their briefs, Petitioners and industry amici stress that generic drug manufacturers need not conduct clinical trials themselves but may rely instead on brand-name manufacturers’ pre-approval studies “to validate the generic product’s safety ...” *Pliva Brief, supra*, at 11. In making this argument, they assume

that the safety profiles of *both* drugs have been definitively established by FDA approval of their marketing and labeling. As demonstrated below, even FDA concedes that they have not.

**A. A Brand-Name Prescription Drug’s Safety Profile is Not Definitively Established Because FDA Approves the Drug**

No prescription drug may be sold in interstate commerce without FDA approval. 21 U.S.C. §§301, *et seq.* (2006). When FDA approves a drug, however, it does not categorically declare that drug safe for all uses and all populations. As Justice Breyer explained in *Levine*, 129 S. Ct. at 1210 (Breyer, J., concurring), FDA approval “does not represent a finding that the drug, as labeled, can never be deemed unsafe by later federal action ... the application of state law,” or evolving science.

Instead, FDA approval simply means that a prescription drug has overcome two regulatory hurdles: first, FDA has approved an Investigational New Drug Application [“INDA”] for specific indications and authorized its manufacturer to begin clinical trials; second, after successful completion of clinical trials, FDA has approved a New Drug Application [“NDA”] for the drug, which includes data from the clinical trials, and has allowed the drug to be marketed in the United States for specified indications and populations. 21 U.S.C. §355(c)(1), (d) (2008).

Even FDA’s own performance reports acknowledge the inherent limitations of pre-approval studies in identifying drug risks. Clinical trials typically study only a few hundred to, at most, 3,000 patients for 6 weeks to 2 years. “The relatively small size required to

make pre-marketing clinical trials practical means that CDER [FDA's Center for Drug Evaluation and Research] cannot learn everything about the safety of a drug before its approval. As a result, a degree of uncertainty always exists about the risks of drugs.”<sup>3</sup> These limitations include samples that are too small to show statistically-significant but catastrophic side effects or trials too short in duration to reveal side effects that develop over time.

Moreover, clinical trials study drugs only in connection with indications specified in the IND/NDA. They cannot study “off-label” uses that develop years after approval. “Off-label” use means prescribing a drug for indications or populations that have *not* been FDA-approved – or evaluated during clinical trials. Off-label use is particularly attractive to manufacturers because it costs little compared to the expense of filing an NDA for a new indication.

The practice is legal and ubiquitous. *Seventy-four percent* of prescriptions for anti-convulsants [like Neurontin] and *sixty percent* for anti-psychotics are for use off-label.<sup>4</sup> The number of these prescriptions for

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<sup>3</sup> FDA, *FY 2009 Performance Report to the President and Congress for the Prescription Drug User Fee Act* (2010), at 106 [“FY 2009 Report”], available at <http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/UserFeeReports/PerformanceReports/PDUFA/ucm228020.htm>.

<sup>4</sup> Randall Stafford, *Regulating Off-Label Use – Rethinking the Role of the FDA*, 358 NEW. ENG. J. MED. 1427, 1428 (2008). Anti-psychotics are the biggest selling drugs in America by therapeutic class, generating \$14.6 billion in sales in 2008, according to industry sources. IMS Servs., *2008 U.S. Sales and Prescription Information*, <http://www.imshealth.com/portal/site/imshealth/menuitem.a46c6d4df3db4b3d88f611019418c22a/?vgnextoid=85f4a56216a10210VgnVCM10000ed152ca2RCRD&cpse>

children and adolescents doubled to 4.4 million between 2003 and 2006, even though no anti-psychotic, brand-name or generic, had ever been FDA-approved for pediatric use at the time. Thus, for vast segments of the pharmaceutical market, clinical trials are irrelevant to drug safety.

Finally, women, minorities, and the elderly have long been significantly under-represented in clinical trials.<sup>5</sup> If studies do not reflect the patient population, unforeseen safety problems may become apparent after the drug is already marketed, possibly resulting in increased morbidity and mortality for certain patients. This proved to be the case at the end of the 1990's, when eight in ten of the prescription drugs pulled from market were found to pose greater health risks for women than men.

*Id.* at 9. The under-representation of the elderly in clinical trials is even more pronounced, even in trials addressing diseases associated with aging such as Alzheimer's.<sup>6</sup>

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<sup>5</sup>Baylor College of Medicine, Chronic Disease Prevention and Control Research Center, EDICT Project, *Major Deficiencies in the Design and Funding of Clinical Trials: A Report to the Nation on Improving How Human Studies are Conducted* 3 (Apr. 1, 2008), available at [http://www.bcm.edu/edict/PDF/EDICT\\_Project\\_White\\_Paper.pdf](http://www.bcm.edu/edict/PDF/EDICT_Project_White_Paper.pdf)

<sup>6</sup>See, e.g., Jiska Cohen-Mansfield, *Recruitment Rates in Gerontological Research: The Situation for Drug Trials in Dementia May Be Worse Than Previously Reported*, 16 ALZHEIMER DIS. & ASSOC. DISORDERS 279, 279-80 (2002).

While NIH mandates that these groups be proportionately represented as subjects of federally-funded clinical research, most clinical trials still fall well short of inclusion targets and the situation is not improving. *See* Baylor College of Medicine, *supra* note 6, at 21. Worse, because FDA views NIH as the sole agency responsible for addressing disparities in clinical trials, FDA *does not evaluate* whether clinical trials include women or other under-represented populations. *Id.* This omission raises the real possibility that safety data generated in clinical trials will not provide doctors with adequate information concerning the risks posed to under-represented populations.

Even when FDA receives proper data, however, it often lacks the skills to interpret it. In fact, FDA's own Science Board found that FDA lacks sufficient expertise in quantitative methods, such as statistics and biomathematics, to assess the products it regulates effectively or to guide sponsors to design valid and informative studies.<sup>7</sup>

As a result of the deficiencies, the U.S. Government Accountability Office ["GAO"] concluded that 51.5 percent of all approved drugs were associated with serious, post-approval risks, evidenced by labeling changes and withdrawals, that were not recognized before approval.<sup>8</sup>

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<sup>7</sup>FDA, *Science and Mission at Risk, Report of the Subcommittee on Science and Technology* 31, 35 [prepared for FDA Science Board] (Nov. 2007), *available at* <http://www.chpa-info.org/ViewResource.ashx?id=4840>.

<sup>8</sup>GAO, *Drug Safety: Post-Approval Risks 1975-1986* (Apr. 1990), at 3, <http://archive.gao.gov/d24t8/141456.pdf>.

FDA thus concedes that uncovering a prescription drug's safety profile also requires *post-marketing* monitoring.

Although premarket testing discloses a general safety profile of a new drug's comparatively common adverse effects, the much larger patient population and longer period of use associated with the marketing of a drug provides, for the first time, the opportunity to collect information on rare, latent, and long-term effects, some of which may be serious.

FDA, *New Drug and Antibiotic Regulations, Final Rule*, 50 FED. REG. 7452, 7471 (Feb. 22, 1985). To that end, FDA regulations require that all drug manufacturers "establish and maintain records and make reports" to FDA about "[a]ny adverse event associated with the use of a drug in humans, whether or not considered drug related," after a drug has received federal approval, 21 C.F.R. §§314.80(a), (c), (j), and make ongoing ADR reports associated with their drugs. *Id.* §§314.80(c)(2)(i)-(ii), (j); 21 U.S.C. §355(e).

FDA has declared that "the primary objective of the adverse drug experience reporting system is to signal potential serious safety problems with marketed drugs ..." 50 FED. REG. at 7471. Based on receipt of "clinical or other experience, tests, or other scientific data," FDA may decide that an approved drug is no longer safe. 21 U.S.C. §355(e). It may ask that the drug be withdrawn or require revisions to its label "as soon as there is reasonable evidence of an association of a serious hazard with a drug; a causal relationship need not have been proved." 21 C.F.R. §201.80(e); 21 U.S.C. §355(e). These regulations apply to generic drug manufacturers at all stages of a drug's marketing. *See, e.g.*, 21 C.F.R. §§201.57(c)(6); 201.80(e); 314.98(a).

**B. Prescription Drugs May Be Sold in Generic Form Because Brand-Name Drugs Have Lost Their Legal Protections, Not Because Their Safety Profiles Have Been Definitively Established**

When FDA approves the generic equivalent of a brand-name prescription drug, it does not render final judgment that either drug is safe. In fact, the Hatch-Waxman Act prohibits FDA from requiring that generic drug manufacturers conduct any new clinical studies before generic are approved. These manufacturers, however, must file an ANDA and show that their drugs are “bioequivalent” to an FDA-approved drug. 21 U.S.C. §355(j).

Once the ANDA has been approved, the Act affords manufacturers five years of labeling exclusivity for new uses or conditions or patent protection for discoveries capable of being patented but allows competition from generics once these protections end – and often long before. 21 C.F.R. §314.108(b)(2). The Act creates an exception to patent law [and claims of patent infringement] that allows generic drug manufacturers to use brand-name drugs still under patent to obtain bioequivalency data so that they will be ready to market generic equivalents the moment the brand-name manufacturers’ protections end. 35 U.S.C. §271(e)(1).

Generic manufacturers may even seek approval to market generic versions of approved drugs *prior* to the expiration of the pioneer’s patent or period of exclusivity by challenging the patent or certifying that it does not cover their product. 21 U.S.C. §355(j)(2)(A)(vii)(IV). Such applications may be filed

as early as 4 years after approval of an NDA. In fact, most patent challenges today are filed at the four-year mark because the first to file gains six months of exclusivity when generics are permitted to enter the market.<sup>9</sup> Given this short time frame, many drug risks may not emerge until after generics have captured the market, as the drugs discussed below demonstrate.

**C. In Addition to Metoclopramide [Reglan], the Safety Profiles of Other Widely-Used Drugs Have Changed Dramatically Long After Generic Equivalents Were Approved**

As with Reglan, the dangerous side effects of other prescription drugs are often identified years after they “go generic.” The following drug histories demonstrate that it is both improper and dangerous to public health to assume, as Petitioners and their amici would have this Court do, that the safety profile of all generic drugs has necessarily been established upon approval of its ANDA.

**1. Promethazine [Phenergan]**

The history of promethazine illustrates the inability of FDA’s post-marketing monitoring to detect catastrophic side effects, particularly those relating only to the means of administering a drug, even when

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<sup>9</sup>U.S. House of Representatives, Committee on Energy and Commerce, Subcommittee of Commerce, Trade and Consumer Protections, *How Pay-for-Delay Settlements Make Consumers and the Federal Government Pay More for Much Needed Drugs* (Statement of Diane E. Bieri) (Mar. 31, 2009), at 8.

hundreds of reports of those side effects have accumulated for decades in FDA's own database.

Phenergan, the drug that caused Diana Levine's injuries, *see Levine*, 129 S. Ct. at 1191, was the brand name for promethazine hydrochloride.<sup>10</sup> FDA approved its use in injectable form in 1956. *Id.* In June 2000, FDA permitted marketing of generic injectable promethazine. *Id.*, promethazine hydrochloride [ANDA 040372]. Wyeth no longer markets Phenergan. It is available today in only generic form.

Promethazine is an antihistamine.<sup>11</sup> Because it blocks certain neurotransmitters from activating areas of the brain that control nausea and vomiting, it was approved to treat allergic reactions, nausea, and motion sickness.<sup>12</sup> Promethazine, however, contains several irritating substances and also has a low pH compared to human bodily fluids; therefore, it essentially acts as an acid when the two come into

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<sup>10</sup>*See* FDA, Drugs@FDA, Phenergan [NDA 008857], available at <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails>.

<sup>11</sup>Benjamin N. Galpern, *et al.*, *Experimental Research on a New Series of Chemical Substitutes with Powerful Antihistamine Activities: The Phenothiazine Derivatives*, 140 COMP. REND. SOC. BIOL. 361 (1946) (*Fr.*); Chiaki Kamei, *et al.*, *Participation of Histamine in the Step-Through Active Avoidance Response and its Inhibition by H1 Blockers*, 57 JAPANESE J. PHARMACOLOGY 473, 475 (1991).

<sup>12</sup>*See* Julie Golembiewski, *et al.*, *Pharmacological Prophylaxis and Management of Adult Postoperative/Postdischarge Nausea and Vomiting*, 21 J. PERIANESTHESIA NURSING 385, 388 (2006).

contact.<sup>13</sup> In situations like the one involving Diana Levine, promethazine damages an artery, cutting off blood flow to the surrounding areas, resulting in necrosis, gangrene, and amputation. *See Levine*, 129 S. Ct. at 1191. Even if it does not damage an artery, it may still cause nerve damage, phlebitis and thrombophlebitis, abscesses, and tissue necrosis, which may require skin grafts.<sup>14</sup>

Prior to 2006, few clinicians were aware of the dangers posed by “IV push” method of administration of promethazine. Until 2006, there were few published reports of inadvertent intra-arterial injection or extravasation<sup>15</sup> associated with promethazine. In fact, “[a] search of the primary literature ... produced no reports of extravasation of promethazine.”<sup>16</sup> Another commentator writes that “[e]mergency department nurses are asked frequently to give this medication intravenous push, yet many are unaware of the risks associated with this practice and the serious outcomes

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<sup>13</sup>*See* Susan Paparella, *The Dangers of Intravenous Promethazine Administration*, 33 J. EMERGENCY NURSING 53, 54 (2007).

<sup>14</sup>*See* Baxter Pharms., *Phenergan Injection* (2005), [http://www.baxter.com/products/anesthesia/anesthetic\\_pharmaceuticals/downloads/phenergan.pdf](http://www.baxter.com/products/anesthesia/anesthetic_pharmaceuticals/downloads/phenergan.pdf).

<sup>15</sup>“Extravasation” is the inadvertent administration of medication outside the vein and into the surrounding tissue. Carmel Sauerland, *et al.*, *Vesicant Extravasation Part I: Mechanisms, Pathogenesis, and Nursing Care to Reduce Risk*, 33 ONCOLOGY NURSING FORUM 1134, 1134 (2006).

<sup>16</sup>*See* Mark A. Malesker, *et al.*, *Extravasation of I.V. Prothazone*, 56 AM. J. HEALTH-SYS. PHARMACY 1742 (1999).

that may occur with intravenous administration.” Paparella, *supra* note 13, at 55.

In August 2006, the Institute for Safe Medication Practices [“ISMP”], a well-respected scientific organization, published the first comprehensive report on the dangers of intravenous use of promethazine. ISMP recommended that promethazine be contraindicated for intravenous use, or that special precautions be used to avoid extravasation.<sup>17</sup>

Despite the absence of prior published reports, ISMP also concluded that there had been individual, unpublished reports of serious injuries associated with the intravenous use of promethazine for decades. “Promethazine extravasations that result in serious tissue damage are not rare; indeed, one in five respondents reported awareness of such an occurrence in their facility with the past five years.”<sup>18</sup> Government data supports ISMP’s conclusion.

ADR reports submitted to FDA are available to FDA, manufacturers, and the public in the Adverse Events Reporting System [“AERS”] database. *See* <http://www.fda.gov/cder/aers/default.htm>. It reveals that, from 1969 [when records were first kept] until December 2006, 45.6% of the serious adverse event reports for intravenous promethazine involved reactions related to those listed in the ISMP report. This is compared to 15.7% of serious adverse events for other intravenous drugs involving similar reactions, a

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<sup>17</sup>*See* ISMP, *Action Needed to Prevent Serious Tissue Injury with IV Promethazine* (Aug. 10, 2006), <http://www.ismp.org/newsletters/acutecare/articles/20060810.asp>.

<sup>18</sup>*See* ISMP, *Promethazine Conundrum: IV Can Hurt More Than IM Injection!* (Nov. 2, 2006), <http://www.ismp.org/newsletters/acutecase/articles/20061102.asp>.

strong signal. There is no indication that FDA ever analyzed this data, kept on its own database, which revealed serious problems associated with intravenous administration of promethazine.

In September 2009, *53 years* after FDA first approved injectable promethazine, *9 years* after FDA permitted the marketing of its generic equivalent, *3 years* after the ISMP study was published, and *6 months after this Court memorialized Phenergan's catastrophic side effects in Levine*, 129 S. Ct. at 1191, FDA finally acted and required a “black box” warning, its strongest, for injectable promethazine concerning the risks the ISMP report revealed.<sup>19</sup>

## 2. SSRI Antidepressants

The history of SSRI antidepressants shows how tort lawsuits acted as a catalyst for the development of antidepressants' safety profile, uncovering critical data withheld by SSRI manufacturers, and moving an unduly-recalcitrant FDA to require appropriate, scientifically-substantiated, and life-saving warnings.

Prozac is the brand name for fluoxetine hydrochloride and the first of a class of SSRI antidepressants. *See Drugs@FDA, supra*, Prozac [NDA 018936]. In 1987, Prozac was approved for treatment of depression, anxiety, and other mood disorders in adult patients. *Id.* Generic forms of Prozac were first

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<sup>19</sup>*See* 21 C.F.R. §201.80(e); FDA, *Information for Healthcare Professionals - Intravenous Promethazine and Severe Tissue Injury, Including Gangrene* (Sept. 16, 2009), <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHealthcareProfessionals/ucm182169.htm>.

approved in 2001. *Id.*, fluoxetine hydrochloride [ANDA 074803].

Approved in 1992 for the same indication, Paxil is the brand name for paroxetine hydrochloride, another member of the SSRI antidepressant class. *See id.*, Paxil [NDA 020031]. Generic paroxetine hydrochloride was first approved for these indications in July 2003. *Id.*, paroxetine hydrochloride [ANDA 075356].

Scientists first recognized that suicidal thoughts and behaviors might occur because of the use of SSRIs themselves, rather than because of the underlying disease of depression, when two prominent Harvard psychiatrists published a study of fluoxetine in 1990.<sup>20</sup> They observed, “[we have recently observed several complex patients who appear to have had serious paradoxical responses to fluoxetine [Prozac] that were characterized by intense, violent suicidal thoughts... the strong obsessive suicidal thoughts apparently emerged *de novo* after weeks or months of treatment.” *Id.* at 209. In the years that followed, evidence of a link between SSRIs and suicide risks only grew stronger.

Nevertheless, the only mention of suicide in Prozac’s initial labeling appeared in a precaution: “[t]he possibility of a suicide attempt is inherent in major depressive disorder and may persist until significant remission occurs.”<sup>21</sup> Other antidepressant manufacturers later copied this language for their own labels. For the next seventeen years, there was no

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<sup>20</sup>See Martin Teicher, *et al.*, *Emergence of Intense Suicidal Preoccupation During Fluoxetine Treatment*, 147 AM. J. PSYCHIATRY 207 (Feb. 1990).

<sup>21</sup>See *Rimbert v. Eli Lilly & Co.*, 577 F. Supp.2d 1174, 1180-81 (D. N.M. 2008).

indication in any antidepressant label that SSRIs could be a part of the problem, rather than a part of the cure.

When two citizen petitions seeking withdrawal of Prozac or inclusion of suicide warnings arrived at FDA in 1990 and 1991, respectively, it responded by convening its Psychopharmacologic Drugs Advisory Committee. Despite the *Teicher* study, the Committee concluded that it had insufficient data to require any warning that Prozac could cause suicidal thoughts or actions.<sup>22</sup> This was true, in part, because of the poor quality of the data the Committee received. *Id.* at 185 (“We agree the data are not great quality data”). Although FDA asked Lilly “to develop plans to conduct new studies, including clinical trials and epidemiological studies, studies that could provide more direct answers to the questions that have been raised,” no such studies were ever conducted or submitted to FDA. *Id.* at 128. FDA took no action against Lilly for its defiance.

Instead, even FDA looked to the courts to assist it in gaining answers and information. In response to the citizen petitions, it wrote that “an actual court finding of a causal relationship” would be significant in its decision-making. “In that event, the agency would be able to evaluate the scientific basis for the court’s conclusion, and consider whether the court’s conclusion warranted a modification of its own position.”<sup>23</sup>

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<sup>22</sup>FDA, Psychopharmacological Drugs Advisory Committee, *Hearing Transcript*, at 126 (Rockville, Maryland) (Sept. 20, 1991), available at <http://www.fda.gov/ohrms/dockets/ac/prozac/2443T1.PDF>.

<sup>23</sup>Letter from Carl C. Peck, M.D. to Sanford Block, Executive Director of Citizens Commission on Human Rights (July 26, 1991), available at <https://ecf.wyd.uscourts.gov/doc1/20715400>

Such a ruling would be a long time coming. For almost a decade, lawyers fought to wrest information from SSRI manufacturers about suicide risks while some manufacturers took extraordinary – and even fraudulent – measures to hide it. *See Winkler v. Eli Lilly & Co.*, 101 F.3d 1196, 1199 (7th Cir. 1996).

After nine years of struggle in the courts, a unanimous federal jury in Wyoming found that Paxil “can cause some individuals to commit homicide and/or suicide.” *Tobin v. SmithKline Beecham Pharms.*, 164 F. Supp.2d 1278, 1287-88 (D. Wy. 2001). This verdict was based on the trial court’s finding that the plaintiff’s suicide evidence was “scientifically reliable” and admissible under *Daubert v. Merrell Dow Pharms.*, 509 U.S. 579 (1993). *Tobin*, 164 F. Supp.2d at 1283.

By 2003, even Wyeth, the manufacturer of Effexor, another SSRI, sent out a “Dear Doctor” letter in which it warned of hostility and suicidality for pediatric patients taking Effexor XR, another SSRI antidepressant.<sup>24</sup> Other manufacturers later did the same with regard to adult patients.<sup>25</sup>

Finally, in 2004, FDA finally acknowledged what many in the scientific community had known for years. In March, it issued a Public Health Advisory, in which it asked all antidepressant manufacturers to warn

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01; *see Motus v. Pfizer*, 127 F. Supp. 2d 1085, 1100 n.13 (C.D. Cal. 2000), *aff’d*, 358 F.3d 659 (9<sup>th</sup> Cir. 2004).

<sup>24</sup>“Dear Healthcare Professional” Letter from Wyeth (Aug. 22, 2003), *available at* <http://www.antidepressantsfacts.com/2003-08-22-Wyeth-Effexor-kids.pdf>.

<sup>25</sup>“Dear Healthcare Professional” Letter from GSK (May 6, 2006), *available at* <http://www.fda.gov/downloads/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/UCM153413.pdf>.

about increased suicide risks for both children and adults.<sup>26</sup> Later that year, FDA requested that manufacturers of antidepressants add a “black box” warning to their respective labels, titled “Suicidality in Children and Adolescents.”<sup>27</sup> FDA’s Director of the Office of Drug Evaluation explained: “I think that we now all believe that there is an increase in suicidal thinking and action that is consistent across all the [SSRI] drugs...”<sup>28</sup>

In 2007, twenty years after FDA first approved Prozac, 16 years after studies revealed SSRIs’ suicide risks, and six years after FDA approved the first generic SSRI, FDA finally requested that labels for all antidepressants include a class-wide section in which the “black box” would be changed from “Suicide in Children and Adolescents” to “Suicidality and Antidepressant Drugs.”<sup>29</sup>

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<sup>26</sup>FDA, *Public Health Advisory* (Mar. 22, 2004), available at <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/PublicHealthAdvisories/ucm161696.htm>.

<sup>27</sup>FDA, *Labeling Change Request Letter for Antidepressant Medication* (Oct. 15, 2004), available at <http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm096352.htm>.

<sup>28</sup>Gardiner Harris, *F.D.A. Links Drugs to Being Suicidal*, THE N.Y. TIMES (Sept. 14, 2004), available at [http://www.nytimes.com/2004/09/14/health/14depress.html?\\_r=1&oref=slogin](http://www.nytimes.com/2004/09/14/health/14depress.html?_r=1&oref=slogin).

<sup>29</sup>The current version of the class-wide section of the label appears at [http://www.fda.gov/cder/drug/antidepressants/antidepressants\\_label\\_change\\_2007.pdf](http://www.fda.gov/cder/drug/antidepressants/antidepressants_label_change_2007.pdf).

### 3. Gabapentin [Neurontin]

Gabapentin's history reveals how its suicide risks were hidden for years from the public, the medical community, and FDA by Neurontin's manufacturer's public denials and illegal promotion of its wide-ranging off-label use in the general population.

Neurontin is the brand-name for gabapentin. It was approved only for "adjunctive" therapy [use with another drug] for epilepsy in adults in 1993. See *Drugs@FDA, supra, Neurontin [NDA 020235]*. Although Parke-Davis, a division of Warner-Lambert, had filed patent applications for Neurontin for treatment of depression, neurodegenerative disease, mania, and bipolar disease, it never sought FDA approval for any of these indications. *In re Neurontin Mktg. & Sales Practices & Prods. Liab. Litig.*, 612 F. Supp.2d 116, 122 (D. Mass. 2009). FDA later denied Warner-Lambert/Pfizer's application for approval of Neurontin as monotherapy for partial seizures, as well as their efforts to increase its maximum dosage.<sup>30</sup> Without FDA approval, federal law prohibited these manufacturers from marketing or promoting Neurontin for these "off-label" uses. Against this backdrop, FDA approved the use of generic gabapentin in 2003. *Drugs@FDA, supra, gabapentin [ANDA # 075350]*.

Evidence of an association between the use of gabapentin and depression and suicidal thoughts and

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<sup>30</sup>See *In re Neurontin Mktg. & Sales Practices & Prods. Liab. Litig.*, 618 F. Supp.2d 96, 103 (D. Mass. 2009). In May 2002, FDA did approve Neurontin for management of post-herpetic neuralgia (pain resulting from nerve damage caused by shingles or herpes zoster) in adults. *Drugs@FDA, supra, Neurontin [NDA 021397]*.

behaviors emerged as early as Neurontin's pre-approval clinical trials in 1992. Because Neurontin was to be used only in a very limited population [adult epileptics], however, FDA found Neurontin "approvable with appropriate and prominent labeling *for use in a specific population*."<sup>31</sup> Thus, in 1994, Neurontin's label included only mention of depression and "suicide gesture" as adverse events observed during clinical trials.<sup>32</sup>

Beginning in 1995, however, Warner-Lambert, later Pfizer, Neurontin's manufacturer, began illegally to promote the sale of Neurontin for "off-label" uses, such as the treatment of pain, bipolar disorder and anxiety. *In re Neurontin*, 618 F. Supp.2d at 102. Warner-Lambert ultimately pleaded guilty to improper promotion of off-label use, among other offenses, and paid a \$430 million fine in June 2004, the year after FDA permitted marketing of generic gabapentin.<sup>33</sup>

During this illicit national marketing campaign, Warner-Lambert/Pfizer not only failed to disclose or warn that Neurontin may be associated with depression and suicidality, their representatives favorably compared Neurontin with competing drugs which had specific suicide warnings. *Id.* at 103. Worse, Pfizer's

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<sup>31</sup>See *In re Neurontin*, 618 F. Supp.2d at 102 (quoting FDA approval of Neurontin NDA) (emphasis supplied).

<sup>32</sup>Drugs@FDA, *supra*, Neurontin, [NDA 020235]; *In re Neurontin Mktg. & Sales Practices & Prods. Liab. Litig.* 2010 U.S. Dist. LEXIS 116876, \*11-12 (D. Mass. Nov. 3, 2010).

<sup>33</sup>See *In re Neurontin*, 618 F. Supp.2d at 104; U.S. Department of Justice, *Press Release: Warner-Lambert to Pay \$430 Million to Resolve Criminal & Civil Health Care Liability Relating to Off-Label Promotion* (May 13, 2004), available at [http://www.justice.gov/opa/pr/2004/May/04\\_civ\\_322.htm](http://www.justice.gov/opa/pr/2004/May/04_civ_322.htm).

Senior Medical Director denied *any* association between Neurontin and suicidality on National Public Radio in 2003: “[T]here is ***absolutely no evidence*** that Neurontin ... has been associated with suicidal behavior or that it can cause suicidal behavior.” *Id.* (emphasis supplied). As a result of Warner-Lambert/Pfizer’s promotion of Neurontin and denial of its dangerous side effects, sales of Neurontin for a host of indications and populations sky-rocketed. *Id.* Approval to market generic equivalents was granted that year.

By January 2008, the side effects of Neurontin and its generic counterparts could no longer be concealed. Fifteen years after Neurontin was approved for limited use in specific populations, and five years after generic substitutes were approved for limited indications, FDA finally issued an “alert” warning physicians to “[b]e aware of the possibility of the emergence or worsening of depression, suicidality, or any unusual changes in behavior” in patients taking gabapentin. *In re Neurontin*, 2010 U.S. Dist. LEXIS 116876, at \*23.

#### 4. Isotretinoin [Accutane]

The history of isotretinoin illustrates how critical safety information about prescription drugs can be masked for years behind inadequate warnings and manufacturers’ efforts to withhold information.

Accutane is the brand-name for isotretinoin, developed by Roche and approved by FDA in 1982 to treat recalcitrant nodular acne. Drugs@FDA, *supra*, Accutane [NDA 018662]. Several generic equivalents of Accutane have been approved by FDA, starting in April 2002. *Id.* Roche withdrew Accutane from the

market in 2009.<sup>34</sup> Only generic substitutes are available today.

Prior to receiving FDA approval to market Accutane, Roche conducted several studies that revealed potential stomach and/or intestinal side effects. In one clinical study of 523 patients, 21.6 percent reported some gastrointestinal problems associated with using Accutane.<sup>35</sup> Pre-approval animal studies also revealed gastrointestinal bleeding in dogs that were administered the drug. *Id.* Nevertheless, FDA approved Accutane without requiring that Roche include warnings about inflammatory bowel disease [“IBD”] in its original label. *Id.* at \*13.

IBD describes a chronic inflammation of the small bowel and the colon. *Id.* at \*3. It typically presents as one of two diseases: Crohn’s disease or ulcerative colitis. *Id.* Ulcerative colitis is a chronic inflammation and ulceration of the inner lining of the cells of the colon and rectum. *Id.* Crohn’s disease is similar to ulcerative colitis but can attack any part of the digestive tract. *Id.* IBD is a permanent condition, although the symptoms may remit and recur. *Id.* It often requires removal of the colon. *Id.*

In 1983, FDA received a citizen petition seeking enhanced warnings on Accutane about a variety of adverse reactions, including IBD. *Id.* at \*14. The petition asserted that “clusters of serious reactions [from ADR reports] are unlikely to be related to factors

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<sup>34</sup>See *Roche Discontinues and Plans to Delist Accutane in the U.S.* (June 29, 2009), [http://www.rocheusa.com/portal/usa/search?communityId=re7180004&search\\_input=accutane&file\\_type=&\\_requestid=321420](http://www.rocheusa.com/portal/usa/search?communityId=re7180004&search_input=accutane&file_type=&_requestid=321420).

<sup>35</sup>See *Kendall v. Hoffman-La Roche, Inc.*, 2010 N.J. Super. LEXIS 1904, \*4 (App. Div. Aug. 5, 2010) (unpublished).

other than the drug.” *Id.* Despite these reports, FDA did not require any change in Accutane’s labeling.

In March 1984, however, Roche itself made very modest revisions to its warnings and physician information about Accutane. In both, it stated only that Accutane had been “temporally associated” with IBD. See *Kendall*, 010 N.J. Super. LEXIS 1904 at \*15; *Drugs@FDA, supra*, Accutane [Labels]. Having donned this regulatory burqa, Roche apparently felt free to ignore the link between isotretinoin and IBD. It never conducted any studies or clinical trials on IBD during the remaining years it sold Accutane.

Roche’s early internal reports, however, revealed “38 case reports of colitis and proctitis in association with [isotretinoin] treatment.” *McCarrell v. Hoffman La Roche, Inc.*, 2009 N.J. Super. LEXIS 558, \*16 (App. Div. Mar. 12, 2009) (unpublished). Roche’s physician reviewer thus recommended that “Roche ... further monitor closely cases of colitis and proctitis reported in association with [isotretinoin] treatment.” *Id.* at \*16-17. A later reviewer announced, after uncovering 104 cases of colitis and related symptoms, that “it is reasonable to conclude from these data, that in rare cases, [isotretinoin] may induce or aggravate a preexisting colitis.” *Id.* at 15.

It is unclear if the ADR reports Roche reviewed made it to FDA in a timely fashion. In 1998, FDA issued a warning letter to Roche for failing to submit serious adverse event reports to FDA regarding Accutane in a timely manner when it was revealed that FDA had not received from Roche some ADR reports regarding Accutane, dated in 1991, until 1997.<sup>36</sup>

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<sup>36</sup>James O’Donnell, *et al.*, DRUG INJURY: LIABILITY, ANALYSIS, AND PREVENTION 348 (2005).

In 2000, 18 years after its approval, FDA approved a label change for Accutane, removing the word “temporally” from the description of IBD and warning that the symptoms of IBD “have been reported to persist after Accutane treatment has stopped ...”<sup>37</sup>

In 2006, four years after FDA approved generic isotretinoin, Massachusetts General and University of Chicago Hospitals issued a comprehensive study of isotretinoin and IBD.<sup>38</sup> The authors obtained every pertinent MedWatch report filed with FDA and reviewed all ADR reports filed with Roche involving isotretinoin and IBD. *Id.* at 1569-70. The study concluded that “in the cases reported to the FDA between 1997 and 2002, isotretinoin appears to be a potential precipitant of IBD.” *Id.* at 1572. The authors recommended warning doctors and patients about these side effects.

It was not until 2010, however, 18 years after Accutane’s approval, 8 years after generics were first approved, and one year after Accutane was removed from the market, that an independent epidemiological study was published that showed a statistically-significant increase in the risk of ulcerative colitis, a form of IBD, with isotretinoin use.<sup>39</sup>

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<sup>37</sup>FDA, Drugs@FDA, Accutane [Labeling Revision] (May 5, 2000), *available at* [http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label\\_ApprovalHistory](http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory).

<sup>38</sup>*See* Deepa Reddy, M.D., *et al.*, *Possible Association Between Isotretinoin and Inflammatory Bowel Disease*, 101 AM. J. GASTROENTEROLOGY 1569 (2006).

<sup>39</sup>Seth D. Crockett, *et al.*, *Isotretinoin Use and the Risk of Inflammatory Bowel Disease: A Case-Control Study*, 105 AM. J. GASTROENTEROLOGY 1986, 1990, 1991 (2010) (finding also that higher doses of isotretinoin augment UC risk).

If this Court shields generic isotretinoin manufacturers from tort liability, they will have no incentive to update their labeling to reflect this new and important information and there is no longer a brand-name manufacturer to communicate this information for them.<sup>40</sup> Petitioners do not tell this Court who will warn patients and doctors if the remaining generic manufacturers do not.

What should be clear from these histories is that it often takes decades before a drug's safety profile fully emerges, sometimes long after generics have supplanted their brand-name counterparts. Second, they show that FDA action has historically reflected and recognized a drug's evolving safety profile, not defined it. Equally important, they illustrate FDA's limited ability actually to protect the public against pharmaceutical risks, particularly in the face of drug manufacturers' efforts to conceal those risks, and the crucial role the tort system has played in uncovering critical drug safety information.

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<sup>40</sup>Once name-brand manufacturers remove their products from the market in favor of generics, there is often no listing at all for either the brand-name drug or its generic equivalents in the PDR, the "Bible" on prescription drugs for most physicians. Without such listings or other communications, the typical dermatologist, who would most likely prescribe isotretinoin, is unlikely to see the *AMERICAN JOURNAL OF GASTROENTEROLOGY*, a specialty journal.

## II. FDA ALONE CANNOT ENSURE GENERIC DRUG SAFETY BECAUSE IT *STILL* LACKS ADEQUATE INFORMATION, RESOURCES, AND AUTHORITY TO MONITOR AND PROTECT THE PUBLIC AGAINST PHARMACEUTICAL RISKS

Petitioners and their industry amici resurrect the argument, rejected in *Levine*, 129 S. Ct. at 1199, that drug labels approved by FDA constitute both a “ceiling” and “floor” on what information manufacturers are required to present to doctors and patients about approved drugs. Unless FDA is freed from the meddling of judges and juries, they contend that it will be unable to strike the proper balance between drug safety and efficacy and public health will suffer.

As demonstrated above, however, FDA has historically *relied* on the tort system to uncover critical drug safety information. In fact, this Court has recognized that “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.” *Id.* at 1202.

Equally important, in making their argument, Petitioners and their *amici* rely on three assumptions, none of which has any basis in FDA’s actual operations. First, they assume that FDA has the necessary time, resources, and tools to fulfill its responsibilities; second, that FDA receives or can acquire sufficient information to strike the proper balance between safety and efficacy; and third, that it has sufficient authority both to acquire missing information and to enforce its requests. All three assumptions are incorrect.

## A. FDA's Responsibilities Far Outstrip the Resources It Has to Address Them

FDA regulates products constituting 25% of the U.S. gross domestic product,<sup>41</sup> including more than 11,000 drugs through CDER.<sup>42</sup> FDA approves several hundred new and generic drugs each year and analyzes hundreds more. FY 2009 Report at 103. Yet, as this Court has recognized, “[F]DA has limited resources to monitor the 11,000 drugs on the market...” *Levine*, 129 S. Ct. at 1202. Since *Levine*, the problem has only grown worse.

CDER has recently experienced a dramatic increase in workload, particularly with regard to generic drugs. The number of ANDAs has almost doubled over the past 6 years, a period when staffing levels increased by only 20%. FY 2009 Report at 6, 82, 92. In FY 2009, CDER approved, or tentatively approved, 599 applications to market generic versions of prescription drugs, the equivalent of *more than two approvals and tentative approvals each business day of the year*. *Id.* at 103. In sum, CDER took 2,006 actions in FY 2009, including approvals, tentative approvals, not approvable, and approvable actions on applications, compared to 1,934 in FY 2008. *Id.* at 103.

Once a drug is approved, FDA's responsibilities for monitoring drug safety mount. The number of adverse

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<sup>41</sup>Bruce M. Psaty & R. Alta Charo, *FDA Responds to Institute of Medicine Drug Safety Recommendations – In Part*, 297 JAMA 1917, 1917-19 (2007).

<sup>42</sup>FDA, CDER, *2005 Report to the Nation: Improving Public Health Through Human Drugs* 12 [“FDA 2005 Report”], <http://www.fda.gov/downloads/AboutFDA/.../CDER/.../UCM078935.pdf>.

event reports submitted to CDER annually reached over 522,871 in FY 2008 and was projected to be over 600,000 by FY 2010. *Id.* at 83. Increasingly, FDA receives citizen petitions for FDA actions on ANDAs. *See* 21 C.F.R. §10.30. Citizen petitions may be used by stakeholders outside of FDA to ask it to take – or refrain from taking – action. FDA has received numerous petitions asking it not to approve particular generic drugs unless certain criteria set forth in the petitions are met. In most cases, these petitions raise scientific issues relating to the standards for approval of ANDAs. CDER must evaluate and respond to each of these petitions. *See* FY 2009 Report at 83.

In addition, there are more than 6,000 FDA-regulated drug manufacturing facilities worldwide for FDA to inspect. *Id.* at 105. This crushing burden has led FDA to engage in regulatory triage. It explained: “FDA’s current performance metric for quality is focused on optimizing the allocation of a limited drug inspection force and increasing the number of inspections among those facilities rated as high risk.” *Id.* Thus, in FY 2008, FDA’s Office of Regulatory Affairs conducted just 132 foreign site pre-approval inspections. *Id.* at 83.

Finally, FDA is also responsible for food safety and protecting the public from a rising tide of food and drug imports. In 2007, the United States imported more than \$2 billion worth of FDA-regulated products, from roughly 200 countries or territories, using 825,000 importers, through over 300 U.S. ports-of-entry.<sup>43</sup>

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<sup>43</sup>FDA, Office of International Programs, Murray Lumpkin, Deputy Commissioner, *Embassy Briefing* (Dec. 1, 2009), available at <http://www.fda.gov/InternationalPrograms/InternationalCommunications/EmbassyBriefings/ucm202894.htm>.

It is little wonder that three recent analyses of FDA’s drug safety oversight – two by GAO and one by IOM – criticized FDA’s inability to keep unsafe drugs off the market and to respond effectively to observed hazards.<sup>44</sup> In particular, IOM observed:

FDA does not have adequate resources or procedures for translating preapproval safety signals into effective post-marketing studies, for monitoring and ascertaining the safety of new marketed drugs, for responding promptly to the safety problems that are discovered after marketing approval, and for quickly and effectively communicating appropriate risk information to the public.

IOM Report at S1-2-1-3c. It *still* does not.

### **B. FDA’s Post-Marketing Monitoring Is Insufficient to Protect the Public Against Pharmaceutical Risks**

Contrary to what many in the public believe, FDA itself does not perform any independent studies or clinical trials on either the new or generic drugs it approves. Instead, it relies on information received from manufacturers during the INDA, NDA, and ANDA processes and on “[a] passive and largely voluntary system of adverse event reporting to monitor the safety

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<sup>44</sup>See GAO, *Drug Safety: Improvement Needed in FDA’s Post-market Decision-Making and Oversight Process* (2006), <http://www.gao.gov/cgi-bin/getrpt?GAO-06-402> [“GAO 2006 Report”]; GAO, *Drug Safety: FDA’s Oversight of the Promotion of Drugs for Off-label Uses*, <http://www.gao.gov/news.items/d088835.pdf>; Institute of Medicine of the Nat’l Academy of Science, *The Future of Drug Safety* (Baciu, Alina, *et al.*, eds., 2006) [IOM Report”].

of drug products on the market.” FY 2009 Report at 107. Both sources are fatally flawed.

As demonstrated above, inherent and practical limitations on the information FDA receives from clinical trials mean that the safety profile of a drug cannot be fully known when FDA approves it.

Even when a drug is approved, however, FDA is still at the mercy of others to supply it with information on the safety of approved drugs. Janet Woodcock, CDER’s Director, the office responsible for monitoring prescription drug safety, described FDA’s historic approach to post-approval monitoring as follows: “you [the manufacturer] do the clinical trial, throw the drug over the wall [from FDA’s perspective], and then send us your Medwatch reports and let us know what happens.”<sup>45</sup>

FDA attempts to monitor drugs’ post-approval performance by gathering reports of ADRs through its AERS and “MedWatch” programs. 21 C.F.R. §310.305 (2008). The Government recognizes, however, that only about 1% of actual adverse drug reactions is ever reported to FDA or manufacturers.<sup>46</sup> Even when reports are received, however, they may be of limited utility

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<sup>45</sup>Catherine Varmazis, *CDER Stresses “Active” Post-Approval Surveillance*, BIO.ITWORLD.COM (June 16, 2008) (quoting Janet Woodcock), available at <http://www.postapproval.org/articles.htm>.

<sup>46</sup>See, e.g., Veterans Health Administration, Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel, *Review of the Efficacy and Safety of Propoxyphene* 8, n.15 (March 2006), <http://www.pbm.va.gov/Clinical%20Guidance/Drug%20Class%20Reviews/Propoxyphene,%20Drug%20Review.pdf>; FDA, CDER, *The Clinical Impact of Adverse Drug Event Reporting* 5 (1996), <http://www.fda.gov/medwatch/articles/medcont/medcont.htm>; IOM Report at 53.

since FDA ordinarily does not receive information about how many people use the drug so that it can calculate the incidence of the ADR.<sup>47</sup>

Worse, there is a growing consensus that some information is simply not accessible from spontaneous reporting systems, such as the long-term effects of medications, reliable comparisons between products, and rare adverse effects associated with older drugs, the ones most likely to have generic equivalents.<sup>48</sup> Phenergan is a tragic example of this deficiency. Moreover, although spontaneous reporting can assist in signal detection for rare cases of severe toxicity, it is less effective in detecting adverse events that commonly manifest in the general population, such as cardiovascular complications of COX-2 inhibitors such as Vioxx. *Id.* at 433, n.18.

These deficiencies are especially problematic because of FDA's historic inability to order and insure that manufacturers actually conducted and submitted post-approval studies. GAO 2006 Report at 28. FDA estimated that 1,231 post-approval studies were overdue as of September 2005, more than 75% of which had not even been initiated.<sup>49</sup> As demonstrated below,

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<sup>47</sup>See Charles Steenburg, *The Food and Drug Administration's Use of Post-Marketing (Phase IV) Study Requirement: Exception to the Rule?*, 61 FOOD & DRUG L.J. 295, 298, n.30 (2006).

<sup>48</sup>David B. Ridley, *et al.*, *Spending on Postapproval Drug Safety*, 25 HEALTH AFFAIRS 429, 433 n.17 (2006), available at <http://content.healthaffairs.org/content/25/2/429.full>.

<sup>49</sup>See FDA, *Report on the Performance of Drug and Biologics Firms in Conducting Post-Marketing Commitment Studies*, 71 FED. REG. 10978-79 (2006).

even FDA's new authority to order post-approval studies may not measurably improve this situation.

### **C. New FDA Authority is Inadequate to the Ensure Generic Drug Safety**

Congress passed the FDAAA in 2007 to improve post-marketing monitoring and prescription drug safety. As CDER's Director explained: "It's a response by Congress to what they saw as FDA's weaknesses."<sup>50</sup> Yet even she admits that FDA's new authority is quite limited and unlikely to remedy the problems it was intended to solve. This, this Court should not assume that FDAAA's passage renders FDA capable of ensuring drug safety without the support of the tort system<sup>51</sup>

Although the FDAAA empowers FDA to order post-approval studies or clinical trials from drug manufacturers, it can do so only under very limited circumstances. 21 U.S.C. §355(o)(3)(A), (B). Dr. Woodcock explained: "We have to make a finding that the study is really needed because we can't find the information out in other ways," *FDA's Woodcock on FDAAA, supra*, that is, FDA must find that its *own* "active postmarket risk identification and analysis system" will be "insufficient" for the purpose. 21 U.S.C. §355(o)(3)(D)(i). Moreover, manufacturers can appeal such orders. *Id.* §355(o)(3)(F).

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<sup>50</sup>*FDA's Woodcock on FDAAA*, CLINPAGE CLINICAL TRIAL NEWS (May 27, 2008), [http://www.clinpage.com/article/fdas\\_woodcock\\_on\\_fdaaa/C9](http://www.clinpage.com/article/fdas_woodcock_on_fdaaa/C9) (quoting Janet Woodcock).

<sup>51</sup>The facts giving rise to the cases before this Court occurred before the effective date of the FDAAA. As a result, it does not apply in them.

Similarly, the FDAAA authorizes FDA to notify drug manufacturers when it becomes aware of safety information it believes should be included in drug labeling and to order a change. *Id.* §355(o)(4)(A). The manufacturer can propose label changes or notify FDA that none is warranted. *Id.* §355(o)(4)(B). If FDA disagrees with the response, it must initiate “discussions” with the manufacturer. *Id.* §355(o)(4)(C). Thus, FDA must still “rel[y] on the prospect of productive negotiations with industry,” a process that “leaves potentially critical regulatory action vulnerable to a subjective and highly variable process of exercising individual or agency influence, and to the vicissitudes of changing politics and attitudes toward regulation,” the approach IOM criticized in 2006. IOM Report at S-9.

While negotiations may last only 30 days; FDA has the power to grant extensions. 21 U.S.C. §355(o)(4)(D). If the parties cannot agree, FDA may order the manufacturer to comply. *Id.* §355(o)(4)(G). Dr. Woodcock notes, however, “but – here again – are the caveats. The sponsor can appeal this.” *FDA’s Woodcock on FDAAA, supra*; 21 U.S.C. §355(o)(4)(F). The FDAAA does not, therefore, give FDA the power to act unilaterally or immediately. At best, it can “accelerate” already-protracted timelines. *Id.* §355(o)(4)(H).

The FDAAA also purports to establish a massive, multi-source health database that will “compile pharmacoepidemiological data through electronic medical health records [EMRs] and medical claims databases” and cover *100 million Americans* by 2012.<sup>52</sup> Yet only 13 percent of doctors and 7.6 percent of

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<sup>52</sup>Kelly Davis, *et al.*, *New Directions in Monitoring Post-Approval Drug Safety*, GOOD CLINICAL PRACTICE JOURNAL 14, 15 (May 2009).

hospitals in the United States currently have *access* even to basic electronic record systems; the figures are lower (4 percent and 1.5 percent, respectively) for comprehensive, fully-functional systems.<sup>53</sup> Worse, health data is dispersed among multiple providers and insurers in both the public and private sectors. Medicare patients, on average, see six different doctors per year.<sup>54</sup> Thus, FDA must somehow marshal these fragmented data into a useful resource.<sup>55</sup> With just \$11.2 *million* in its 2008 budget for modernizing drug safety, it is unlikely FDA can do so.

Moreover, FDA does not have legal authority to require diverse entities to make data available for post-marketing monitoring because of privacy and constitutional concerns.<sup>56</sup> Questions of due process and accountability could chill private-sector willingness to

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<sup>53</sup>Catherine DesRoches, *et al.*, *Electronic Health Records in Ambulatory Care – A National Survey of Physicians*, 359 *NEW ENG. J. MED.* 50, 56 (2008); Ashish Jha, *et al.*, *Use of Electronic Health Records in U.S. Hospitals*, 360 *NEW ENG. J. MED.* 1628, 1632 (2009).

<sup>54</sup>U.S. House of Representatives, Subcommittee on Ways and Means, *Promoting Disease Management in Medicare* (Apr. 16, 2002) (statement of Dr. Gerard Anderson), at 5.

<sup>55</sup>See Carol C. Diamond, *et al.*, *Collecting and Sharing Data For Population Health: A New Paradigm*, 28 *HEALTH AFFAIRS* 454, 456, 460 (2009); Richard Platt, *et al.*, *The New Sentinel Network – Improving the Evidence of Medical-Product Safety*, 361 *NEW ENGL. J. MED.* 645, 647 (2009).

<sup>56</sup>See Mark A. Rothstein, *Health Privacy in the Electronic Age*, 28 *J. LEGAL MED.* 487, 489 (2007); Nicholas P. Terry & Leslie P. Francis, *Ensuring the Privacy and Confidentiality of Electronic Health Records*, 2007 *U. ILL. L. REV.* 681, 700 (2007) (discussing privacy concerns with large health databases).

participate. Without their participation, monitoring will be no better in the future than it is today.

Yet even if FDA can collect this data, “figuring out how to analyze the data is going to be [FDA’s] problem. It’s going to be harder than anyone thinks,” and particularly, “difficult to do until we have better analytic tools.” *FDA’s Woodcock on FDAAA, supra*. As demonstrated above, it lacks those tools today.

For these reasons, the FDAAA did not provide FDA with the information, resources, or authority that would be essential to establish conclusively drug safety profiles or to protect the public from pharmaceutical risks without the critical assistance of the tort system.

## CONCLUSION

The decisions of the courts below should be affirmed.

Respectfully submitted,

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