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The Drug Safety System Conundrum

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I. INTRODUCTION

The current turmoil over drug safety is substantially broader in scope and deeper in impact than previous turning points created by new drug laws enacted in response to relatively isolated prescription drug tragedies.[1] Now, an array of prescription drugs is associated with inadequate safety documentation and surveillance, high-profile market withdrawals, and regular Congressional and media criticism of Food and Drug Administration (FDA) diligence and corporate behavior regarding the management and mitigation of serious adverse drug reactions. Adverse reactions to prescription drugs have become the most common iatrogenic cause of patient injury[2] and are estimated to elicit over 700,000 emergency room visits, over two million hospitalizations and over 100,000 fatalities in the U.S. annually.[3] Approximately 4 percent of hospitalized patients experience a clinically significant adverse drug reaction,[4] and, according to FDA, approximately 300,000 adverse drug reactions annually in hospitals are preventable.[5]

Increasingly, the reason behind the drug safety turmoil as well as central to the evolution of the drug safety debate is deepening personal injury, false advertising, failure to warn, business practice and class-action litigation from consumers, investors and government agencies against pharmaceutical marketers. Litigation discovery has documented and/or has convinced courts and juries that serious problems exist and ethical lapses have occurred in the drug safety system. These failures combined with now regular publicity about pharmaceutical litigation and sometimes stunning revelations of impropriety contained in litigation discovery are focusing and sustaining academic and political attention on pharmaceutical risk identification and communication. Moreover, further projecting pharmaceutical litigation into the drug safety system, FDA often delays new label warnings, "Dear Doctor" letters, requests for new safety research and requests for market withdrawals until hundreds or even thousands of product liability lawsuits are filed and many are adjudicated successfully for plaintiffs, sensationalized by accusatory media reports and editorials, and brought to the attention of Congress. Delays in drug safety mitigation, which are driving the drug safety issue, are increasingly due to the likely adverse impact of contextualizing drug safety issues with pharmaceuti-

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[1] The sulfanilamide contamination of the 1930s producing the Federal Food, Drug, and Cosmetic Act of 1938 (FDCA) requiring the FDA safety review of new drugs prior to approval and the thalidomide-induced birth defects of the early 1960s producing the 1962 Kefauver-Harris Drug Amendments requiring drug manufacturers to prove efficacy FDA prior to FDA approval.

[2] B.L. Strom, *How the U.S. Drug Safety System Should Be Changed*, JAMA 295, 2072-2075, (2006).

[3] J. Lazarou, B. H. Pomeranz & P. N. Corey, *Incidence of Adverse Drug Reactions in Hospitalized Patients,* JAMA 279, 1200-1205, (1998); *Food and Drug Administration, Strengthening Drug Safety*, *FDA Consumer Health Information*, (May 31, 2007), www.fda.gov/consumer/features/drugsafety0607.html, (last accessed July 9, 2007).

[4] G. K. Al-Tajir & W. N. Kelly, *Epidemiology, Comparative Methods of Detection, and Preventability of Adverse Drug Events,* ANN. OF PHARMACOTHERAPY 39, 1-6, (2005).

[5] FDA Drug Safety Initiative: Fact Sheet, www.fda.gov/oc/factsheets/initiative.html, (last accessed July 9, 2007).

cal litigation and media coverage, which in turn lead to intensified congressional consideration for new drug safety legislation. Because pharmaceutical litigation poses such a substantial barrier to improving the drug safety system, progress toward a better drug safety system is improbable without wider consideration of the impact and future of pharmaceutical litigation and its substantive mitigation by pharmaceutical companies.

The financial stakes for the pharmaceutical industry regarding drug safety and corporate vitality are substantial. In 2006, U.S. prescription drug sales reached $274.9 billion, fueled in part by the new Medicare Part D drug benefit program[6] while U.S. research spending by the prescription pharmaceutical industry reached $55.2 billion, and the 2005 estimated cost to develop a new drug for marketing was $899 million.[7] Out of 5,000 to 10,000 screened compounds, about 250 enter preclinical testing, five enter clinical trials, and one is approved by FDA—a 10 to 15 year process.[8] High-profile market withdrawals of high-revenue prescription drugs spurred by the notoriety of life threatening drug reactions identified after FDA approval and broad patient use have cost the pharmaceutical industry billions of dollars in lost annual revenues (e.g., Vioxx, Bextra, Baycol, Rezulin, Lotonex, Propulsid, Seldane, Pondimin, Redux). Resulting litigation and its associated costs against the pharmaceutical industry have virtually exploded in recent years. For example, over the past two years, Merck has spent approximately $1 billion for its defense of Vioxx against over 27,000 product liability and associated class action lawsuits (to date, fewer than 20 have reached trial). In April of this year, FDA rejected approval of Merck's planned Vioxx successor, Arcoxia, representing a zero return on Merck's research investment largely due to adverse press about Vioxx litigation.[9] In inevitable response to ongoing controversy disseminated by the media and arising from the medical community concerning weaknesses in the current drug safety system, Congress has conducted numerous hearings into FDA's drug safety inadequacies and has drafted many proposals to amend current law, create new law, and intensify financial and criminal punishments for corporate compromises in drug safety.[10] Within a week after the House's Committee on Oversight and Government Reform hearing on June 6, 2007, assessing FDA inadequacies

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[6] Press release. IMS Reports U.S. Prescription Sales Jump 8.3 percent in (2006), to $274.9 billion. www.imshealth.com/ims/portal/front/articleC/0,2777,6599_3665_80415465,00.html, (last accessed July 9, 2007).

[7] Accenture report developed for the Pharmaceutical Research and Manufacturers of America (PhRMA). In Pursuit of High Performance through Research and Development: Understanding Pharmaceutical Research and Development Cost Drivers, www.accenture.com/Global/Research_and_Insights/By_Industry/Health_and_Life_Sciences/Pharmaceuticals_and_Medical_Products/PharmaceuticalCostDrivers.htm., (last accessed July 9, 2007).

[8] PhRMA Key Industry Facts, www.phrma.org/key_industry_facts_about_phrma, (last accessed July 9, 2007).

[9] K. Rawson, *The Death of Arcoxia: Drug Regulation in a "Whistleblower" Climate*, The RPM REPORT 2, 2-9, (2007).

[10] C.D. Furberg, A.A. Levin, P.A. Gross, R.S. Shapiro, & B.L. Strom, *The FDA and Drug Safety: A Proposal for Sweeping Changes*, ARCH INT MED 166, 1938-1942, (2006); Senate bill S1082, http://thomas.loc.gov/cgi-bin/query/D?c110:7:./temp/~c110e5yoha::, (last accessed July 9, 2007); Senate bill S468, http://thomas.loc.gov/cgi-bin/query/D?c110:3:./temp/~c110e5yoha::, (last accessed July 9, 2007); Senate bill 1024, http://thomas.loc.gov/cgi-bin/query/D?c110:1:./temp/~c110e5yoha::, (last accessed July 9, 2007); Senate bill S484, http://thomas.loc.gov/cgi-bin/query/D?c110:5:./temp/~c110e5yoha::, (last accessed July 9, 2007); House bill HR788, http://thomas.loc.gov/cgi-bin/query/D?c110:2:./temp/~c110e5yoha::, (last accessed July 9, 2007); House bill HR2273, http://thomas.loc.gov/cgi-bin/query/D?c110:4:./temp/~c110e5yoha::, (last accessed July 9, 2007); House bill HR1561, http://thomas.loc.gov/cgi-bin/query/F?c110:6:./temp/~c110e5yoha:e865:, (last accessed July 9, 2007).

pertaining to the postmarketing safety surveillance of Avandia and FDA's same-day announcement requesting Avandia's marketer (Glaxo SmithKline) to include a "black box" label warning regarding an Avandia side effect of heart failure, the media reported that plaintiff attorneys were mobilizing against Glaxo SmithKline for personal injury and investor class-action litigation.[11]

Much depends on the outcome of the sharpening debate about the drug safety system, particularly the postmarketing surveillance of adverse drug reactions of new prescription drugs, and specific ways that Congress will decide to augment FDA responsibilities and authorities. The stakeholders—patients, pharmaceutical industry, insurance industry, heathcare professionals, media and various government agencies—all want or need something from FDA, typically something different on any particular drug safety matter. More robust than ever before, the voices pushing FDA and its congressional oversight are organized, relatively well funded, and determined. Accordingly, the yet-to-be-completed public policy process is more complicated than ever. Leadership collaboration between the private and public sectors to solve weaknesses in the drug safety system has perhaps never been so important for the economic outlook of and people's confidence in prescription pharmaceuticals.

II. THE ELEPHANT IN THE ROOM

That the merit of adverse drug reactions in particular or in general depends on one's perspective is hardly more demonstrable than in the contentious arena of pharmaceutical litigation whose impact on drug safety public policy is becoming increasingly powerful as a result of the strengthening voices of determined litigants and the medical community. An inconsistent patchwork of FDA drug safety regulations and enforcement combined with a virtual explosion of pharmaceutical litigation has pushed the pharmaceutical industry into a highly defensive position costing several billions of dollars annually for infrastructure, defensive clinical research and public relations, litigation expenses, and congressional lobbying efforts. In the characteristically animated arena of litigation, adverse drug reactions can be cast either as prima fascia proof of causation or the inane basis for frivolous litigation supported by nothing more than junk science. Their meaning becomes mired by vested interests, controversy, vicious attacks and counter-attacks, personal threats, and sometimes, because of substantial product liability implications, wholesale denial of relevance (which may or may not be meritorious). Differential diagnosis, clinical trials, peer-reviewed case reports, and consensus reviews of case report series are subjected to criticism as junk science. Expert witnesses enter the battle on both sides—one group testifying that the adverse drug reaction can happen, the other group testifying that it cannot.[12] While such battles are the grist of the adversarial process of litigation, and at times with FDA, they also increasingly complicate the public policy of drug safety. For example, many FDA decisions and

[11] M. Flood, Drug Doubts Put Lawyers, Pharmaceutical Companies in Motion, CHRON.COM, (June 9, 2007, www.chron.com/disp/story.mpl/business/4875810.html, (last accessed June 19, 2007); Glaxo faces first class action suit over Avandia; R. Lindsay, Law Firm Claims GlaxoSmithKline Mislead Investors by not Making Public its Study of the Risks of the Diabetes Drug, TIMES ONLINE, (June 12, 2007), http://business.timesonline.co.uk/tol/business/industry_sectors/health/article1921199.ece, (last accessed July 9, 2007).

[12] T.N. Tiedt, *Expert Witnesses in Product Liability Litigation: Boon or Bust?* FDLI UPDATE. (May/June 2005).

internal policy directions concerning adverse drug reactions, including new drug application review, are the direct result of pharmaceutical litigation.

The metastasizing process and managerial critical mass of pharmaceutical litigation sometimes overtly and sometimes insidiously are steering the public policy of drug safety. Participants in the deepening litigation quagmire are increasingly lobbying Congress to legislatively benefit their respective litigation positions, likely undermining cohesive repair of a system recognized to be inadequate. One of the ways that pharmaceutical litigation is steering the drug safety discussion while simultaneously providing ammunition for critics of the drug safety system is through a few widely publicized examples of remarkable revelations during the discovery phase of litigation during which massive internal stores of company documents and executive depositions are examined, e.g., identification of previously unavailable safety data withheld from FDA and/or the medical community, questionable managerial response by a drug's marketer, hostility toward FDA, and clear demonstrations of flaws in the existing drug safety system regarding high-profile adverse drug reactions.[13] Cases of delay in reporting adverse drug reactions to FDA, minimizing drug risks in published studies, and questionable clinical research practices have induced medical journal editorial boards to reshape their policies over the past few years pertaining to manuscript conclusions and potential conflicts of interests of authors. The Director of the National Institutes of Health (NIH) banned its scientists from accepting compensation from the biomedical industry and called for an ethics summit.[14] In some cases, pharmaceutical litigation plays a substantive role in market withdrawal of various high-revenue prescription drugs and in corporate restructuring and redefining corporate procedures pertaining to adverse drug reactions. A possible example of a conflict of interest by FDA regarding post-approval identification of an adverse drug reaction, FDA is actively supporting drug companies' litigation defense by arguing that drug marketers should not communicate any risk about drugs beyond FDA-approved labels and that FDA approval should preempt legal action against drug marketers concerning alleged inadequacies in product warnings (note: state and federal judges sometimes rule against the preemption position of FDA and the pharmaceutical industry).[15] In addition, corporate intimidation of the medical community via lawsuits filed or threatened by pharmaceutical companies against medical "opinion leaders" and their universities likely has a chilling effect on the medical community's involvement with drug safety public policy.[16]

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[13] J. Avorn, *Paying for Drug Approval—Who's Using Whom?*, NEJM 356, 1697-1700, (2007); J. Avorn, *Evaluating Drug Effects in the Post-Vioxx World: There Must be a Better Way*, CIRCULATION 113, 2173-2176, (2006); H. Markel, *Why America Needs a Stronger FDA*, JAMA 294, 2489-2491, (2005); C. D. Furberg, *See* 10; P. B. Fontanarosa, *See* 35; C. T. Struve, *See* 35; A. S. Kesselheim, *See* 38.

[14] D. Willman, *NIH Chief Calls for Ethics Summit*, LOS ANGELES TIMES, (Feb. 12, 2005), www.latimes.com/features/health/medicine/la-na-nih12feb12,1,3869183.story?coll=la-halth-medicine&ctrack=1&cset=true, (last accessed July 9, 2007).

[15] THE ASSOCIATED PRESS, *Judge: U.S. Approval of Drug Label Does not Clear Manufacturer of Claims*, INTERNATIONAL HERALD TRIBUNE, (July 9, 2007). www.iht.com/articles/ap/2007/07/03/america/NA-GEN-US-Vioxx-Federal-Cases.php, (last accessed July 9, 2007); L. A. Johnson, *Judge's Ruling in Prempro Case Stops Wyeth "Pre-emption" Strategy*, NEWSDAY.com, www.newsday.com/news/local/wire/newjersey/ny-bc-nj--wyeth-premprosuit0627jun27,0,6992921,print.story?coll=ny-region-apnewjersey, (last accessed July 9, 2007); S. Korris, *Drug Makers Must Warn Patients of Risks, Justices Rule*, (June 28, 2007), www.wvrecord.com/news/197357-drug-makers-must-warn-patients-of-risks-justices-rule, (last accessed July 9, 2007).

[16] For example; John Buse, M.D., Ph.D., President of the American Diabetes Association and Director of Diabetes Care and the University of North Carolina School of Medicine, testified before the House Committee on Oversight and Government Reform June 6, 2007 that the Chairman of Smith-

Already expensive and not to be ignored is the fact that a substantial business momentum has developed for at least hundreds of plaintiff and defense law firms increasingly in perpetual pharmaceutical litigation mode. Consultant companies assemble evidence and public relations packages, expert witness opinions, and repositories of expert witnesses and "opinion leaders." To insinuate "independent" support for a related body of cases, law firms have created *ad hoc* trade, medical and scientific associations with annual budgets and boards of directors. Specialty law firm networks and a tendency toward multi-district litigation management have evolved, supported by marketing agreements with smaller, isolated law firms. Millions of pages of discovery documents in many lawsuits necessitate thousands of attorney and expert witness billable hours to analyze and codify in case motions and expert witness reports. Critical depositions are video-taped, orchestrated and monitored by teams of lawyers across the country. Mock juries and jury consultants are recruited to assess and refine case presentation and credibility of expert witnesses and corporate executives. Websites are created for ready worldwide access to discovery documents, depositions, motions and court rulings. We now have a self-sustaining litigation support enterprise with billions of dollars of annual revenues, and this represents a vested interest in the status quo and in the complexification of the drug safety system.

Thousands of patients and investors, and several state and federal government agencies sue pharmaceutical companies, costing litigants several billions of dollars annually for medical evaluations, product testing, trial preparation, expert witnesses, case settlements, court awards and jury verdicts for injury liability and punitive damages, corporate restructuring, augmenting FDA negotiations for product labeling and new drug clinical research planning, and reduced profitability resulting from adverse media, expanded label safety warnings, and market withdrawals. The amalgamated impact—financial, human resource and societal—of pharmaceutical litigation is clearly substantial. Until the drug safety system improves and adverse publicity and litigation wane, pharmaceutical litigation likely will expand further in a vicious cycle of identification of a new risk followed by a litigation expansion, thereby further stressing the legal system and the highly defensive pharmaceutical industry as well as creating an even larger need for an improved drug safety system. Real improvement in the drug safety system is unlikely unless the vicious cycle is broken.

III. DRUG SAFETY SYSTEM UNDER ASSAULT

Increasingly over the past two decades and now dramatized by exploding pharmaceutical litigation and its derivative sensational media coverage, pressures have been mounting for re-appraisal and overhaul of the surveillance of adverse drug reactions, particularly after marketing approval of a new prescription drug by FDA

Kline Beecham Pharmaceutical Research and Development threatened Dr. Buse and the University of North Carolina with a lawsuit for the company's market capitalization loss of billions of dollars allegedly resulting from a one-minute mention to a group of physicians in 1999 by Dr. Buse that Avandia may be associated with a risk of heart failure (similarly recognized in 1999 by FDA's medical officer managing the Avandia NDA and ultimately requested by FDA of Glaxo SmithKline June 6, 2007). Moncef Slaoui, Ph.D., Glaxo SmithKline's current Chairman of Research and Development conceded before the House Committee June 6, 2007 that the matter should have been handled differently by his predecessor at SmithKline Beecham. *See* http://oversight.house.gov/story.asp?ID=1325, http://oversight.house.gov/documents/20070606112934.pdf, and http://oversight.house.gov/documents/20070606133312.pdf, (last accessed July 9, 2007).

and the associated expansion and diversification in a drug's use compared to that examined during premarketing clinical trials. In view of the magnitude of adverse drug reactions, pharmaceutical litigation, adverse publicity, declining confidence in FDA and corporate behavior, and the financial stakes for pharmaceutical marketers and their shareholders, the drug safety system turmoil must now be addressed.

FDA is the target for much of the criticism of the current drug safety system, particularly because many stakeholders perceive an increase in postmarketing discovery of serious adverse drug reactions trapped in FDA red tape for unreasonable periods of time. At FDA, about two-thirds of its drug reviewers lack confidence in FDA,[17] and about one in five feels pressured toward drug approval.[18] The Government Accountability Office (GAO) found that "FDA lacks clear and effective processes for making decisions about, and providing management oversight of, postmarket safety issues."[19] The Institute of Medicine (IOM) stated: "The approval decision does not represent a singular moment of clarity about risks and benefits associated with a drug. … "[20] IOM criticized FDA for its lack of clear regulatory authority, chronic underfunding, impotent postmarketing safety monitoring, and mission politization. According to ex-FDA Commissioner Mark McClellan, "We have no active drug-surveillance system."[21] Seriously lagging FDA resources and authorities[22] as well as widely publicized criticism of FDA performance provide easy picking for consumer activists, the media and the cyclical political storm. Predictably, public confidence in FDA is declining: negative ratings were given by 58 percent of consumers in 2006, compared to 37 percent in 2004.[23] Congress and FDA exacerbate problems in the drug safety system by budgeting merely 6.7 percent of $437.8 million in FDA user fees to modernize the drug safety system for 2008, while $274.9 billion were spent on prescription drugs in 2006.[24] Complicating FDA's drug safety management task are laws enacted that further challenge FDA enforcement resources, e.g., the Dietary Supplement and Health Education Act of 1994 (DSHEA),[25] which effectively eliminated drug safety protections when many drugs are now marketed as nutritional supplements. It took FDA years of investigation, administrative procedure, and analysis of substantial product litigation and corporate discovery documents and depositions to eventually ban ephedra "nutritional supplements."[26] Interestingly, the rapidly expanding nutritional supplement industry

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[17] B. M. Psaty & S. P Burke, *Protecting the Health of the Public—Institute of Medicine Recommendations on Drug Safety*, NEJM 355, 1753-1755, (2006).

[18] FDA's review process for new drug applications: a management review. Wash., DC, Department of Health and Human Services (HHS), (2003) (Publication no. OEI-01-01-00590).

[19] Drug Safety: improvement needed in FDA's posmarket decision-making and oversight process. Wash., DC, GAO, (Mar. 2006) (Report no. GAO-06-401).

[20] Committee on the Assessment of the U.S. Drug Safety System, A. Baciu, K. Stratton, S.P. Burke, eds., *The Future of Drug Safety: Promoting and Protecting the Health of the Public*, Wash., DC, NATIONAL ACADEMIC PRESS, (2006).

[21] M. McClellan, *Drug Safety Reform at the FDA—Pendulum Swing or Systematic Improvement?*, NEJM 356, 1700-1702, (2007).

[22] E.E. Slater, *Today's FDA*, NEJM 352, 293-297, (2005).

[23] C.D. Furberg et al, *See* 10.

[24] S. Hennessy & B.L. Strom, *PDUFA Reauthorization—Drug Safety's Golden Moment of Opportunity?*, NEJM 356, 1703-1704, (2007).

[25] *See* DSHEA, P.L. 103-417, 103rd Congress; T. N. Tiedt, *At the Crossroads: the Dietary Supplement Health and Education Act*, FDLI UPDATE, (May/June 2003); T. N. Tiedt, *The Dietary Supplement Health and Education Act: Use it or Lose it*, FDLI UPDATE (May/June 2002).

[26] 69 Fed. Reg. 6787-6854, (2004), Final Rule Declaring Dietary Supplements Containing Ephedrine Alkaloids Adulterated Because they Present an Unreasonable Risk.

is increasingly viewing itself as a safer treatment of disease than prescription drugs and is critical of FDA for inadequate attention to prescription drug safety.

Depositions, trial testimony, attorney arguments and court rulings emanating from the pharmaceutical litigation process often contain harsh criticism of FDA's handling of adverse drug reaction reports, and embarrassingly demonstrate generalized FDA inadequacy compared with a large pharmaceutical company's vastly superior productivity and skill in marshaling expertise and recruiting academic "opinion leaders."[27] Moreover, attorneys for plaintiffs and defendants attempting to capitalize on FDA inadequacies are increasingly pressuring FDA to produce witnesses, documentation, and collaboration.

Much of the problem in the drug safety system is explained by differences between premarketing and post-approval drug use by patients. During premarketing clinical trials, adverse drug reaction experience is effectively constrained because of many safeguards protecting patients during the clinical trial for a relatively small number of patients treated with a new drug for a relatively short duration of therapy compared to a drug's use after widespread marketing. While only a few thousand patients are exposed to the new drug in aggregate before approval, millions of patients, many of whom have significantly more complex medical histories than those studied prior to approval, will ultimately use the drug in intended as well as untested circumstances after approval. Individual premarketing clinical trials examine only a few dozen or few hundred carefully selected research patients who, because of numerous enrollment disqualifications, generally have more homogenous medical histories and more limited patient demographics. Accordingly, post-approval drug exposure is substantially more diverse, and finding new adverse drug reactions during drug marketing missed during premarketing clinical trials is a predictable outcome, making direct comparisons of adverse drug reactions between research patients and post-approval real world patients challenging.[28] Fifty-one percent of all approved drugs elicit at least one serious type of adverse reaction that was not observed during premarketing clinical trials leading to a post-approval label change; 20 percent of new drug labels are modified with a black box warning; 3 to 4 percent of new drugs are withdrawn for safety reasons.[29] Serious adverse drug reactions that occur with a frequency of one in 1,000 patients or less will predictably remain undetected until post-approval use. Most clinically relevant adverse drug reactions occur at a rate of one in 10,000 or less.[30] For example, FDA estimated that Pondimin/Redux-induced pulmonary hypertension occurred less than once in 10,000-person-years of drug use.[31]

Another problematic aspect of the drug safety system, itself a 60-year-old passive system of collecting spontaneously-generated adverse drug reactions, is that numerous conflicts of interest are built into the system (FDA's Medwatch system—where approximately 400,000 non-systematically generated adverse reaction reports having varying quality and relevance are submitted annually to FDA—more than 90 percent of these reports are from drug manufacturers, while

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[27] E.E. Slater. *See* 22.

[28] B.L. Strom. *See* 2.

[29] U.S. GAO FDA Drug Preview: Post-Approval Risks, 1976-1985, Wash., DC: U.S. GAO; (Apr. 16, 1990); *See* 2; *See* 19.

[30] F.O. Ajayi, H. Sun, & J. Perry, *Adverse Reactions: a Review of Relevant Factors*, J CLIN PHARMACOL 40, 1093-1101, (2000), BASIC AND CLINICAL PHARMACOLOGY, Eighth ed., B.G. Katzung, ed. Lange Medical Books/McGraw-Hill, (2001).

[31] FDA Medical Bulletin, Vol 1, (Mar. 1997), www.fda.gov/medbull/mar97/medwatch.htm, (last accessed July 9, 2007).

about 1 percent of all adverse drug reactions and about 10 percent of all serious adverse drug reactions are reported to FDA).[32] Firstly, FDA may be resistant to conclude that it had made a mistake in approving a new drug or to acknowledge an error in its design approval and analysis of the premarketing clinical trials serving the basis of FDA's new drug approval.[33] Secondly, over 90 percent of the adverse reaction reports submitted to FDA come from the new drug's marketer, who may have an inherent economic conflict of interest in drug safety decisions.[34] The marketer may not adequately acknowledge a risk or fail to implement studies to quantify the risk.[35] Investigators from the national Center for Drug Evaluation and Review published in a leading medical journal that "there are strong disincentives for companies…to identify safety problems with licensed drugs quickly and efficiently. … Seeking out and sharing bad news about a product are unlikely to increase business." [36] As a surrogate of medical opinion, editors for the Journal of the American Medical Society could hardly be more blunt. Responding to industry assurances that "vigorous government oversight … ensures the integrity of data and results," these journal editors concluded, "Despite these assurances, scientific and ethical lapses involving industry and industry-sponsored studies strongly indicate otherwise." [37] Thirdly, in the latest report from FDA to Congress pursuant to the Food and Drug Administration Modernization Act of 1997, FDA informed Congress that two-thirds of marketer commitments to perform postmarketing safety studies negotiated with FDA as a condition of FDA new drug approval remain to be initiated, and only 21 percent were ongoing (by law, FDA cannot enforce these agreements after new drug approval). [38]

More fundamental than the systematic problems at and the legal constraints on FDA there can be inconsistencies in how adverse drug reactions are defined and reported, making clear-cut comparisons among reported cases and quantitative summaries of all the possible case details difficult to accomplish.[39] It is even more

[32] B.L. Strom, *Potential for Conflict of Interest in the Evaluation of Suspected Adverse Drug Reactions: A Counterpoint*, JAMA 292, 2643-2646, (2004); B.M. Bsayt, C.D. Furberg, W.A Ray, & N.S. Weiss, *Potential for Conflict of Interest in the Evaluation of Suspected Adverse Drug Reactions; Use of Cerivastatin and Risk of Rhabdomyolysis*, JAMA 292, 2622-2631, (2004); B.M. Psaty, C.D. Furberg, W.A. Ray, & N.S. Weiss. Authors' reply to Bayer's response to *Potential for Conflict of Interest in the Evaluation of Suspected Adverse Drug Reactions: Use of Cerivastatin and Risk of Rhabdomyolysis*, JAMA 292, 2658-2659, (2004); C.D. Furberg et al, *See* 10.

[33] C.D. Furberg et al, *See* 10.

[34] B.L. Strom, *See* 32.

[35] P.B. Fontanarosa, D. Rennie, C.D. DeAngelis, *Postmarketing Surveillance—Lack of Vigilance, Lack of Trust*. JAMA 292, 2647-2650, (2004); C.T Struve, *The FDA and the Tort System: Postmarketing Surveillance, Compensation, and the Role of Litigation*. YALE J HEALTH POLICY, LAW, AND ETHICS, Vol 5, (Summer 2005).

[36] M.R. Griffin, C.M. Stein, W.A. Ray, *Postmarketing Surveillance for Drug Safety: Surely we can do Better*, CLIN PHARMACOL THER 75, 491-494, (2004).

[37] P.B. Fontanarosa & C.D. DeAngelis, *Conflicts of Interest and Independent Data Analysis in Industry-funded Studies—Reply*. JAMA 294, 2576-2577, (2005).

[38] Food and Drug Administration Modernization Act of 1997 (FDAMA). Pub L No. 105-115 Stat 2296 (1997); *See* C.D. Furberg et al, *See* 10; A.S. Kesselheim & J. Avorn, *The Role of Litigation in Defining Drug Risks*, JAMA 297, 308-311, (2007).

[39] However, their individual or combined contribution is not necessarily negated. While medical journals limit the number of published adverse event reports to minimize redundancy and generally impose a word limit on case reports, adverse drug reaction cases have long been important teaching vehicles and relied upon as peer-reviewed examples of causation or misdiagnosis. *See* T. Brewer & G. A. Colditz, *Postmarketing Surveillance and Adverse Drug Reactions: Current Perspectives and Future Needs*, JAMA 281, 824-829, (1999); J.P. Vandenbroucke, *In Defense of Case Reports*, ANN INTERN MED 134, 330-334, (2001); M.N. Gharaibeh, H.E. Greenberg & S.A. Waldman, *Adverse Drug Reactions: A Review*. DRUG INFO J 32, 323-338, (1998); P.C. Hannaford & V. Owen-Smith, *Using Epidemiological*

difficult to fully satisfy all concerned with case report evaluation and usage, causing substantial debate during pharmaceutical litigation. Case reports of adverse drug reactions differ in quality, relevance, format, and audience. Substantial differences exist among case reports submitted to FDA, to medical journals, to a pharmaceutical company, as the basis for a lawsuit, from consumers, from healthcare professionals, and increasingly from attorneys and pharmaceutical company employees. Accordingly, case inconsistencies typically generate voluminous motions, argument, expert witness testimony and court rulings in pharmaceutical litigation. Particularly problematic is the lack of a "denominator" (X number of adverse events (numerator) divided by total number of adverse events (denominator)—the ratio, a measure of risk). Collating adverse events will quantify a "numerator." However, without a "denominator," relative frequency and derivative statistical estimates of risk magnitude cannot be calculated[40] (however, risk of one drug compared to another can be estimated).[41] Further uncertainty regarding case assessment derives from the fact that the nature of all adverse drug reactions is not identical.

Accordingly, assigning equal merit or demerit to all adverse drug reactions and their case reports would be a mistake. Some adverse drug reaction cases represent predictable consequences of the drug's known pharmacology and expected toxicity, especially for those drugs that impact diverse receptor systems and/or critical physiological processes (e.g., the cardiovascular or central nervous systems), exemplifying real and sometimes tragic consequences from drug exposure and, therefore, appropriately impacting product marketing and/or compel active surveillance. Such case reports can be especially convincing evidence, i.e., establish risk.[42] Other case reports can describe entirely unexpected phenomenon, although these do not necessarily rule out causation (e.g., thalidomide and birth defects). Some case reports are minor or even trivial, and many case reports are insufficient for decisionmaking. Others are associated with off-label use beyond the control and/or without safety assessment by the marketer, willful abuse, or suicide, all of which might induce an adverse drug reaction profile not matching exactly that recognized in the intended patient population. Undoubtedly, many case reports are frivolous. Amazingly, in view of the long intensity of the adverse drug reaction discussion and its considerable costs, the relative proportions of these categories of adverse drug reactions reports remain unknown.

IV. SOLUTIONS PROPOSED TO REPAIR POSTMARKETING SURVEILLANCE

Because of the magnitude and ramifications of what is now considered inevitable restructuring of the drug safety system, numerous proposals have been widely discussed in the medical literature and during congressional hearings. For example:

Data to Guide Clinical Practice: Review of Studies on Cardiovascular Disease and Use of Combined Oral Contraceptives, BMJ 316, 984-987, (1998).

[40] For example; "relative risk," "odds ratio," "absolute risk" compared to placebo, no treatment, or background risk rate, respectively.

[41] S. Bent, T.N. Tiedt, M.C. Odden & M.G. Shlipak, *The Relative Safety of Ephedra Compared with Other Herbal Products*, ANN INTERN MED 138, 468-471, (2003).

[42] The statistical magnitude of risk generally requires large-scale, resource-intensive cohort or case-control studies typically spanning several years and costing millions of dollars. However, for many clinical endpoints, larger scale studies to quantify the risk may be unnecessary or unethical requirements to reliably associate a drug with an adverse event.

- decouple the drug approval process from the postmarketing drug safety system—perhaps by creating a drug safety board independent of FDA;
- reconsider the proportion of prescription drug user fees paid by drug manufacturers to FDA toward new drug approval;
- create a proactive system of capturing adverse drug reaction experiences to augment the current passive system of mostly voluntary reports by healthcare professionals and patients and one that captures a small fraction of all adverse drug reactions—perhaps by utilizing large databases of patient records, e.g., Departments of Defense and Veterans Affairs, Kaiser-Permanent and the Group Health Cooperative, the Medicare Part D drug benefit program, pharmacy and hospital databases, physician network databases;
- expand FDA drug safety staffing, resources and expertise, including funding for FDA or an independent drug safety board to conduct postmarketing epidemiological studies;
- establish an ongoing initiative to better understand how drug risks are detected and evaluated;
- reconsider the current requirement for sometimes lengthy negotiations between FDA and a drug marketer before new side effects or new characteristics of known side effects appear in product labeling;
- examine the impact of off-label drug use on the pattern of adverse drug reactions in intended patient populations;
- include greater numbers of patients with complex medical histories in clinical trials;
- recognize the adverse reaction potential or likelihood of all pharmacological effects of a drug rather than limit focus on the intended pharmacological effect;
- consider the impact of direct-to-consumer promotion of prescription drugs on altering physician health care delivery and possible over-prescription of a drug;
- consider mandatory requirements of postmarketing safety surveillance negotiated with FDA prior to marketing approval;
- establish a larger permanent network of drug safety centers across the United States to provide actionable data beyond that of the current program involving less than 11 Centers for Education and Research in Therapeutics with an annual budget of $5.9 million;
- consider requirements for comparative safety and efficacy trials of a new drug with established drug therapies;
- consider conditional new drug approval until a substantially larger database of patient use exists than from premarketing clinical trials performed for new drug approval;
- require complete public disclosure of all safety data derived from premarketing and postmarketing clinical trials, adverse reaction reports submitted to FDA, and any pharmacoepidemiological studies performed on a drug;
- encourage greater use by FDA of and drug safety professional access to FDA NDA and IND files; and
- expand the beneficial role of pharmacists to mitigate adverse reactions has been undervalued in public policy. For example; a recent study of nearly two million hospitalized Medicare patients reported that increasing clinical pharmacist staffing rate from about one to about five per one hundred occupied beds for

pharmacist-provided admission drug histories reduced the drug adverse reaction rate by 48 percent. [43] Patients in hospitals without pharmacist-provided adverse event management have substantially more adverse drug events, more deaths, greater Medicare charges, and greater drug costs.

In its recent and to many observers long overdue drug safety initiative, FDA has begun implementing at least some of the recommendations from the IOM.[44] FDA is expanding physician and patient drug safety information, restructuring and evolving the culture of CDRH, creating a drug safety board, modernizing its drug development process, and developing electronic health information.[45] However, because FDA's task to improve drug safety is so monumental and FDA's resources are constrained, concern remains that lackluster FDA leadership poses a barrier as well as commercial problem for pharmaceutical marketers.[46]

Furthermore, given the delays in designing a more effective drug safety system and the substantial financial impact of removing high-profile, high-revenue drugs from the market due to serious adverse reactions accompanied by new rounds of notoriety, FDA will probably face both increasing expectations and criticism. Accordingly, it is virtually impossible to beneficially evolve drug safety public policy without meaningful collaboration from all affected parties.

VI. CONCLUSION

Improved management of adverse drug reactions mandates substantial collaboration among all stakeholders for an improved drug safety system, for a robust pharmaceutical industry, and to better prepare, educate, manage and protect patients. A fundamental paradigm shift is required concerning how adverse drug reactions are identified from reactive to proactive—to shift away from the current passive, un-coordinated, and contentious system toward expanded research designs and expertise to identify and clarify adverse drug reactions earlier as well as revitalize and better fund FDA managerial systems and authorities. An optimized drug safety system is vital for the larger context of healthcare delivery, especially as its future holds so many uncertainties. The elephant in the room—pharmaceutical litigation—must be candidly discussed and skillfully fused into the solution rather than sequestered in the shadows steering drug safety policy. If identifying more adverse reactions unfairly induces more litigation, increasing the effectiveness of drug safety policy will be resisted. Accordingly, the role of pharmaceutical litigation in the planning for ongoing repair of the current system to better manage adverse drug reactions must be more widely examined. Otherwise, little progress is feasible.

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[43] C.A. Bond & C.L. Raehl, *Clinical Pharmacy Services, Pharmacy Staffing, and Adverse Drug Reactions in United States Hospitals*, PHAMACOTHERAPY 26, 735-747, (2006).

[44] FDA's Drug Safety Initiative, www.fda.gov/cder/drugsafety.htm, (last accessed June 3, 2007); The Future of Drug Safety—Promoting and Protecting the Health of the Public: FDA's Response to the IOM's 2006 Report, HHS, FDA, (Jan. 2007), www.fda.gov/oc/reports/iom013007.pdf, (last accessed July 9, 2007).

[45] FDA Drug Safety Initiative: Fact Sheet, www.fda.gov/oc/factsheets/initiative.html, (last accessed July 9, 2007).

[46] R. Baghdadi, *Tone Deaf: FDA Commissioner Hits the Wrong Note*, RPM REPORT, 2, 1-5, (2007).