

**Ethics and Admissibility: Failure to Disclose Conflicts of Interest in and/or Funding of Scientific Studies and/or Data May Warrant Evidentiary Exclusions**

by

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## **Introduction**

The sources of expert testimony in products liability litigation involving the pharmaceutical industry often include clinical trials or other studies funded or otherwise influenced by pharmaceutical companies. Increasing concern exists that the academic medical centers that conduct most drug research are dominated or otherwise unduly influenced by a pharmaceutical industry willing to shape scientific results to protect or promote its products and, as a result, that the scientific data and conclusions of studies on the safety and efficacy of such products may be unreliable. When injured consumers seek to hold the industry accountable through litigation, studies done by researchers with potential conflicts of interest arising from such funding and subsidies are often used against them. Studies produced to facilitate drug approval by the FDA, or produced by researchers with hidden ties to or unduly influenced by pharmaceutical company interests, are potentially excludable from evidence for failure to meet the reliability requirements for admissibility under *Daubert*.

Deployment of relevant legal gate-keeping criteria for exclusion of evidence tainted by undisclosed conflicts of interest may temper the pharmaceutical industry's use of misleading and/or erroneous studies or data influenced by undisclosed sources of funding or other conflicts of interest caused by the pharmaceutical industry involvement. Counsel should ascertain the source of funding, sponsorship, and subsidy of any study sought to be admitted into evidence or utilized in testimony of expert opinion. Industry funding should signal caution and skepticism, with any undue influence brought to the Court's attention to be excluded from evidence in appropriate cases.

This article presents an overview of the extraordinary present-day influence of the pharmaceutical industry in the consumer drug and medical device context, and explores

scientific bias and non-disclosure in two examples: the prescription drug Synthroid and silicone breast implants.

**The Scientific Community is Increasingly Concerned about  
the Prevalence, Significance and Potential Prejudice of Pharmaceutical  
Industry Influence Upon Scientific Research in Academic Research Centers**

Corporate funding of medical research is commonplace, and due to diminishing public funding, an inevitable fact in the future of academic medicine. Catherine D. DeAngelis, MD, Editor of the Journal of the American Medical Association (JAMA), in her November 2000 article *Conflict of Interest and the Public Trust*, noted the “relative paucity” of public funds for clinical research: in 1999 the National Institutes of Health provided \$17.8 billion for research, while the top 10 pharmaceutical companies spent \$22.7 billion.<sup>1</sup> Some academic institutions have entered into partnerships with drug companies for research centers and teaching programs in which students and faculty members perform industry research. For the academic institutions such arrangements provide badly needed funding, and the drug manufacturers get access to research talent and affiliation with a prestigious “brand,” using the reputation of the medical school to bolster the credibility of the industry-funded research.<sup>2</sup> Editorials from the leading medical journals lament increasing industry dominance in academia and the resulting disintegration of peer review and pure scientific hypothesis. Both JAMA and the New England Journal of Medicine published issues highlighting conflict of interest concerns in November of 2000.<sup>3</sup> The New England Journal of Medicine revisited the issue in September of 2001, and JAMA devoted an issue to bias and quality of peer review in June of 2002.<sup>4</sup> Prominent scientists and medical researchers are increasingly raising important issues about potential bias in the manner in which pharmaceutical company-funded research is developed and reported, particularly where pharmaceutical company ties with and financial support of researchers are not disclosed.

A September 2001 New England Journal of Medicine editorial, *Sponsorship, Authorship and Accountability*, a collaboration by the editors of 13 leading national and international medical journals including the Annals of Internal Medicine, JAMA, Canadian Medical Association Journal, Journal of the Danish Medical Association, the Lancet, and MEDLINE, described how competition between academic and private institutions for research funding allows corporate sponsors to dictate the terms of studies and study design, participate in interpretation, and limit access to raw data.<sup>5</sup> Contracts with corporate sponsors often limit an investigator's ability to evaluate data independently or to submit a manuscript for publication without sponsor pre-approval. If the results of a finished trial are unfavorable to a sponsor's product, the results can be suppressed.<sup>6</sup> Such arrangements compromise intellectual inquiry, and conceal the extent to which clinical investigators might have been "powerless to control the conduct of a study that bears their names," making a "mockery of clinical investigation."<sup>7</sup> Studies show an association between corporate sponsorship of clinical research and publication of favorable research results and research that is of a lower quality.<sup>8</sup>

In addition to corporate funding of clinical trials, the New England Journal of Medicine September 2001 editorial described how a conflict of interest may arise when the institution, author, reviewer, or editor of a study has financial relationships with corporate sponsors of academic research.<sup>9</sup> Conflicts of interest include situations of employment, consultancies, stock ownership, honoraria, or paid expert testimony.<sup>10</sup> Researchers commonly serve as consultants to the companies whose products they study, join advisory boards and speaker's bureaus, agree to be listed authors of articles ghostwritten by the interested companies, promote drugs at company-sponsored symposiums, and receive expensive gifts, dinners, and trips to luxurious settings paid for by pharmaceutical sponsors.<sup>11</sup> Relationships between corporate sponsors and

clinical research begins early in medical school with regular gifts to students in the form of doctor's bags, medical textbooks, pharmaceutical logo-embossed office supplies, free lunches, and opulent dinners and social events.<sup>12</sup>

Elizabeth A. Boyd, PhD, and Lisa A. Bero, PhD, from the University of California San Francisco Medical School in their case study, *Assessing Faculty Financial Relationships with Industry*, JAMA Nov. 1, 2000, noted that, while clinical investigators design and interpret clinical trials in academic institutions, the purpose of many clinical trials is “to facilitate regulatory approval of a drug rather than to test a specific novel scientific hypothesis,” thus undermining “traditionally held academic values of intellectual freedom, open exchange of ideas, and research in the interest of the public good.”<sup>13</sup> Public perception of published evidence on the efficacy and safety of pharmaceutical products rests on the assumption, increasingly unwarranted, that clinical-trials data are gathered and presented in an objective manner.<sup>14</sup>

A New England Journal of Medicine study published in November of 2000 analyzed the conflict of interest policies at ten medical schools in the United States concerning significant financial interests of researchers in the companies owning a device or product being studied.<sup>15</sup> These institutions included the Baylor College of Medicine, Columbia University College of Physicians and Surgeons, Harvard Medical School, Johns Hopkins University School of Medicine, the University of Pennsylvania School of Medicine, the University of California at Los Angeles School of Medicine, the University of California San Francisco School of Medicine, the University of Washington School of Medicine, Washington University School of Medicine at St. Louis, and Yale University School of Medicine. Only two universities in the study prohibited researchers from trading stock or stock options in a company that sponsored their research. Of the ten universities in the study, two “ordinarily did not allow faculty

members to participate in clinical research if they had . . . significant financial interest in the company owning the product or device being studied, but exceptions were allowed.”<sup>16</sup> Another study found that 34% of articles published in 14 leading biology and medical journals had authors with undisclosed financial interests in companies related to the research.<sup>17</sup> In addition, academic institutions are paid royalties from patents generated by their faculty, and retain a share of industry research grants.<sup>18</sup>

A November 2000 JAMA study, *Policies on Faculty Conflicts of Interest at U.S. Universities*, from the Stanford University Center for Biomedical Ethics, the University of California San Francisco Institute for Health Policy Studies, and the New York University School of Law, reviewed faculty conflict of interest policies at 89 major U.S. biomedical research institutions.<sup>19</sup> The study found that most policies on conflict of interest lack specificity about the kinds of relationships with industry that are prohibited with wide variation in management of conflicts of interest, causing competition among universities for corporate sponsorship that could erode academic standards and lessen public confidence in university research.<sup>20</sup>

Key to the perceived efficacy of studies and their legal admissibility under *Daubert*, is the process of peer review for publication.<sup>21</sup> However, at the Fourth International Congress on Peer Review in Biomedical Publication held in Barcelona, Spain in September 2001, Drummond Rennie, MD, the Deputy Editor of JAMA, spoke to the quality of “peer reviewed” publications:

. . . despite this system [of peer review] anyone who reads journals widely and critically is forced to realize that there are scarcely any bars to eventual publication. There seems to be no study too fragmented, no hypothesis too trivial, no literature citation too biased or egotistical, no design too warped, no methodology too bungled, no presentation of results too inaccurate, too obscure, and too contradictory, no analysis too self-serving, no argument too circular, no conclusions too trifling or too unjustified . . . for a paper to end up in print.<sup>22</sup>

Douglas C. Altman, DSc of the Cancer Research UK/NHS Centre for Statistics in Medicine in Oxford, England noted in *Poor Quality Medical Research, What Can Journals Do?*, “considerable evidence that many published reports of randomized controlled trials are poor or even wrong, despite their clear importance” and that “poor methodology and reporting are widespread.”<sup>23</sup> He faults the authors of articles for “poor research methods . . . thinly sliced study results, selective reporting, [and] . . . scientific fraud as well as a general tendency to inflate the importance of results.”<sup>24</sup> In the same issue of JAMA, a study from the University of California San Francisco Medical School, *Association of Journal Quality Indicators With Methodological Quality of Clinical Research Articles*, found that randomized controlled trials funded by the pharmaceutical industry had the highest incidence of poor methodological quality and suggested that this be considered in assessment of the usefulness of an article.<sup>25</sup> In some cases articles may be the direct product of a marketing company paid by the pharmaceutical manufacturer, ghostwritten with doctors paid a fee to be the “author.”<sup>26</sup> Additionally, a study reported in the June 5, 2002 JAMA by Steven Woloshin, MD, MS and Lisa M. Schwartz from the Department of Veterans Affairs Medical Center and Center for Evaluative Clinical Sciences at Dartmouth Medical School, *Press Releases: Translating Research Into News*, found that when information is released to the public about new medical findings, press releases do not routinely highlight study limitations, conflicts of interest, or the role of industry funding and often exaggerate the perceived importance of findings.<sup>27</sup>

**Industry and Governmental Partnership at the  
FDA Speeds Drugs to Market with Minimal Regulatory Interference**

Once a drug has been tested, its manufacturer submits the studies to the United States Food and Drug Administration (FDA) for regulatory approval to market the drug. Concurrent with articles in the leading medical journals about pharmaceutical industry undue influence in

academic research settings, leading newspapers including the New York and Los Angeles Times are increasingly discussing conflicts of interest at the FDA and the marketing of drugs without thorough pre-market evaluation and testing, resulting in needless patient deaths and expensive recall. See David Willman, *FDA Minimized Issue of Lotronex's Safety; Health: Times Study Finds Officials Sided With Drug Maker on Regulatory Concerns, Agency Reevaluation is Underway*, The Los Angeles Times (Nov. 2, 2000), Denise Grady, *FDA Pulls a Drug and Patients Despair*, The New York Times (Jan. 30, 2001), Janet Lundblad and Sunny Kaplan, *How a New Policy Led to Seven Deadly Drugs; Medicine: Once a Wary Watchdog, the U.S. Food and Drug Administration Set Out to Become a 'Partner' of the Pharmaceutical Industry. Today, the American Public Has More Remedies But Some Are Proving Lethal*, The Los Angeles Times (December 20, 2000).

Historically, the process of obtaining FDA approval for a new drug was rigorous and time consuming.<sup>28</sup> However, in 1992 under pressure from AIDS activists, the FDA received a new mandate from the presidency for “fast track” drug approval to speed new life-saving therapies to AIDS patients who might not otherwise live long enough to benefit from potentially life-prolonging new drugs.<sup>29</sup> The Clinton administration urged a collaboration between drug companies and FDA regulators as “partners, not adversaries,” a relationship that persists in the pro-business Bush administration.<sup>30</sup> While the fast track policy may be sound when applied to public health crises such as HIV/AIDS, and has undoubtedly benefitted many patients, the extension of “fast track” rules to the approval and marketing of the increasingly popular and aggressively promoted non-life-saving “lifestyle” drugs is of great concern.

Americans spend more than \$100 billion on drugs each year according to the New York Times, *A Muscular Lobby Rolls Up Its Sleeves*, November 2001.<sup>31</sup> The pharmaceutical industry

has 625 registered lobbyists, more than there are members of Congress.<sup>32</sup> It has a combined lobbying and campaign contribution that is larger than any other industry.<sup>33</sup> More than half of the drug industry's lobbyists are either former members of Congress or former Congressional staff and government employees.<sup>34</sup> A new "partnership" between the FDA and the pharmaceutical industry has resulted in the eighteen advisory committees of the FDA that recommend approval having appointees that double as consultants or researchers for the same companies whose products they evaluate.<sup>35</sup> Medical officers at the FDA report declining standards for drug approval and pressure from supervisors to approve new drugs, as well as inappropriate phone calls from manufacturers of drugs under review and interference in the approval process.<sup>36</sup>

The pharmaceutical companies have a strong voice in the FDA, which sets *minimum* requirements for safety. Regulation of drugs does not always protect patients from harmful effects that are downplayed or not researched in the first instance. The fast track drug approval originally meant only for life-saving AIDS drugs has expanded to drugs for many ailments, including drugs for pain, heartburn, and high blood pressure.<sup>37</sup> Fast-track drug approval often occurs at the expense of thorough pre-marketing drug safety and led to the release of at least seven apparently inadequately tested drugs that required recent withdrawal due to association with serious and/or lethal side effects including Rezulin, Lotronex, Propulsid, Raxar, Redux, Posicor, and Duract.<sup>38</sup>

### **The Role of the Plaintiff: Exposing Unreliable Studies**

Litigation against drug manufacturers commonly stems from claims that plaintiffs suffered adverse health effects following exposure to a prescription drug manufactured, sold and/or promoted by a pharmaceutical concern.<sup>39</sup> In an increasingly market-solicitous academic and regulatory environment, any undisclosed funding or conflicts of interest should raise

questions of bias and undue influence when defendants seek to elicit expert testimony based on industry-funded clinical trials or studies.

Under Federal Rule of Evidence 104(a), judges evaluate the general principles or methods by which experts present opinions as to specific causation in preliminary evidentiary hearings to determine admissibility and relevancy before evidence may be presented to the jury.<sup>40</sup> Pharmaceutical companies will often defend themselves with studies used to gain FDA approval for the drugs, showing that the drugs meet minimum standards for safety and efficacy.<sup>41</sup> Expert testimony based on these studies is used to show no sufficient causal link between the plaintiff's illness and the defendant's product.<sup>42</sup> However, because defendants may have steered studies to show efficacy and lack of harm, suppressed evidence of side effects and manipulated data, and/or chose not to fund or design studies that could discover harmful effects, the plaintiff may be the only voice to draw scrutiny to industry-funded studies. If there are any serious questions of reliability due to issues of undue influence or non-disclosure, such evidence should be excluded from evidence under *Daubert* analysis.

**Keeping the Junk Out: a Review of Standards for  
Admissibility Under Daubert and Argument for a New Precedent**

Three U.S. Supreme Court cases define standards for expert testimony, *Daubert v. Merrell Dow Pharmaceuticals*, *General Electric Co. v. Joiner*, and *Kumho Tire v. Carmichael*.<sup>43</sup> *Daubert* is invoked to ban so-called “junk” science from the courtroom, admitting only testimony which is relevant and reliable in the opinion of the court and will assist the trier of fact.<sup>44</sup> Under these principles, undisclosed pharmaceutical company funding of and/or undisclosed influence over and/or ties to medical research data offered in litigation may be subject to potential exclusion by the court as junk science.

Admissibility of expert testimony based on scientific tests and methods in federal and state courts was originally guided by *Frye v. United States*, holding that the basis of expert testimony must have been sufficiently established to gain general acceptance in its particular field.<sup>45</sup> The *Frye* standard was superceded in Federal courts in 1993 when the Supreme Court decided *Daubert v. Merrell Dow Pharmaceuticals*, holding that Federal Rule of Evidence 702 replaced the *Frye* test.<sup>46</sup> FRE Rule 702 states “if scientific, technical, or other specialized knowledge will assist the trier of fact to understand the evidence or to determine a fact in issue, a witness qualified as an expert by knowledge, skill, experience, training, or education may testify thereto in the form of an opinion or otherwise.”<sup>47</sup> Rule 702 was amended in 2000 to reflect the two main requirements of admissible expert testimony set forth by *Daubert*, that it be both relevant and reliable.<sup>48</sup> Expert testimony must be based on sufficient facts or data, be the product of reliable principles and methods, and the expert witness must apply the principles and methods reliably to the facts of the case.<sup>49</sup> The key to exclusion of evidence brought by the pharmaceutical industry lies in this reliability prong of *Daubert*.

Under *Daubert*, the trial judge must determine if the expert will “testify to scientific knowledge that will assist the trier of fact to understand or determine a fact in issue” and assess “whether the reasoning or methodology underlying the testimony is scientifically valid and whether that reasoning or methodology properly can be applied to the facts in issue.”<sup>50</sup> Factors considered in this inquiry include whether the theory or technique can and has been tested; whether it has been subjected to peer review and publication; the known or potential rate of error; and whether the theory or technique is generally accepted by the scientific community.<sup>51</sup> Research conducted in academic clinical trials dominated by a sponsor is arguably neither scientifically valid nor truly accepted by the scientific community. The leading scientific

journals are calling for reevaluation of disclosure and conflicts of interest precisely because pharmaceutical industry influence is damaging intellectual inquiry and scientific hypothesis.

Judge Kozinski, in the Ninth Circuit's decision on remand in *Daubert*, (hereinafter *Daubert II*) further elucidated factors relevant to admissibility:

[Federal judges] must satisfy themselves that scientific evidence meets a certain standard of reliability before it is admitted. This means that the expert's bald assurance of validity is not enough. Rather, the party presenting the expert must show that the expert's findings are based on sound science, and this will require some objective, independent validation of the expert's methodology. . . . While [there is no] definitive checklist or test, the Court [in *Daubert*] did list several factors federal judges can consider in determining whether to admit expert scientific testimony under FRE 702 . . . . One very significant fact to be considered is whether the experts are proposing to testify about matters growing naturally and directly out of research they have conducted independent of the litigation, or whether they have developed their opinions expressly for purposes of testifying.<sup>52</sup>

In evaluating the reliability of testimony of an expert witness, *Daubert II* assumed that an underlying research record prepared for litigation is inherently biased, ignoring the non-litigation sources of research bias.<sup>53</sup> However, a scientist conducting research for a drug manufacturer is arguably no less aware of the result desired by the sponsor than is a researcher conducting similar research in connection with litigation.<sup>54</sup> Accordingly, all sources of research funding should be scrutinized for bias.

*Kumho Tire Co. v. Carmichael* further clarifies the discretion a trial court judge exercises to determine admissibility of expert testimony.<sup>55</sup> The *Daubert* "gate keeping" obligation to exclude unreliable expert testimony allows a trial judge to consider "one or more" of the specific *Daubert* factors.<sup>56</sup> The test for reliability is "flexible," and the factors do not necessarily or exclusively apply to all experts or every case.<sup>57</sup> "The factors mentioned in *Daubert* may or may not be pertinent in assessing reliability depending on the nature of the issues, the expert's particular expertise, and the subject of his testimony. . . . It [is] clear that [the] list of factors was

meant to be helpful, not definitive.”<sup>58</sup> Here it would seem that a trial judge could have the discretion to determine that research bias can be an indication of unreliability.

In 1997 the U.S. Supreme Court decided *General Electric v. Joiner*, which held that the proper standard of trial court rulings on appeal is an “abuse of discretion” standard.<sup>59</sup> This abuse of discretion standard allows the trial judge to look for analytical gaps in scientific methods and conclusions, and to exclude evidence based on the data and the opinion offered if the judge determines that the proffered studies are inadequate to support an expert’s conclusions.<sup>60</sup> An appellate court will not reverse a case unless the ruling is manifestly erroneous, even if it was “outcome determinative,” meaning the decision to allow the expert testimony determined the outcome of the case.<sup>61</sup> These guidelines for appeal would arguably seem to allow an appellate judge to examine the basis of an expert’s testimony, and if it is flawed due to bias and/or funding sources undisclosed, to find a ruling of inadmissibility to stand.<sup>62</sup> A court is allowed to determine if there is too great an analytical gap between the data and the opinion offered.<sup>63</sup> If the data is flawed and the source of the data suspect, it is easy to extrapolate that the study findings or opinion testimony are therefore unreliable due to the science potentially unduly influenced by its sponsor.

Discretion to exclude to exclude expert testimony because of non-disclosure of funding sources or conflicts of interest in the underlying data is within the guidelines set by *Daubert*, *Kumho Tire*, and *Joiner*. Bias is directly relevant to the requirement of reliability, without which the proffered expert testimony may be “junk science.” Such testimony could be excluded for both its unreliability and for public policy reasons of encouraging an open and honest academic and regulatory clinical investigation. Applied proactively, exclusion of unreliable industry

funded studies may be appropriate to protect potential plaintiffs from harmful omissions and hidden manipulation of data crucial to a fair evaluation of the risks of pharmaceuticals.

**Knoll Pharmaceutical Settles Civil Class Action Claims Brought for its Suppression of Clinical Research Evidence of Efficacy of Generic Alternatives to Synthroid**

The Synthroid case is a dramatic example of industry dominance in academia and demonstrates how the pharmaceutical industry may actively manage scientific studies and data to promote its products and increase its profits. Synthroid, a brand-name version of the drug levothyroxine, is a synthetic hormone replacement used in treatment of hypothyroidism, a metabolic disorder caused by inadequate production of a hormone secreted by the thyroid gland.<sup>64</sup> Levothyroxine is an unpatented drug whose sales were historically dominated by Knoll's "Synthroid" brand product, which at one point held roughly 84% of a \$600 million annual market.<sup>65</sup> Synthroid was advertised with the slogan, "there is no substitute for Synthroid."<sup>66</sup>

Synthroid's drug manufacturer, Knoll Pharmaceutical, now a subsidiary of BASF AG, commissioned a study at the University of California San Francisco (UCSF) to examine whether rival versions of levothyroxine were bioequivalent to Synthroid. Bioequivalency means drug absorption levels in the body are equivalent. Bioequivalency would negate the manufacturer's claim that patients could not switch safely from Synthroid to a generic levothyroxine because even if the dosages were equal the effect might differ.<sup>67</sup> As long as Synthroid had no recognized bioequivalent substitute, physicians and pharmacists were unable to switch patients from Synthroid to less expensive alternatives. A generic or other substitute would threaten Synthroid's dominance of the levothyroxine market.

However, the researchers found that each of three versions of levothyroxine were bioequivalent to Synthroid.<sup>68</sup> The results of the study were to be published in the Journal of the

American Medical Association (JAMA).<sup>69</sup> However, as a condition of financing the UCSF study, Knoll required a contract restricting publication of the study results without the sponsor's written consent.<sup>70</sup> Knoll then threatened that publishing the results of the UCSF study would subject UCSF to liability for breach of contract.<sup>71</sup> Knoll sought to discredit the study, despite having paid \$250,000 to finance it, despite peer-review by five independent researchers, and endorsement by JAMA.<sup>72</sup> Less than two weeks before the article about the UCSF study was to be published, UCSF withdrew it citing impending litigation.<sup>73</sup>

Knoll then distributed an industry publication refuting the UCSF study, claiming that its levothyroxine was superior to generic substitutes. The FDA ordered Knoll to cease distribution of the publication because it constituted "misleading labeling," "fail[ed] to reveal facts that are material" and was illegal.<sup>74</sup>

After much damaging publicity, three years after its initial submission for publication, JAMA published the UCSF study, *Bioequivalence of Generic and Brand-name Levothyroxine Products in the Treatment of Hypothyroidism* in the April 16, 1997 issue.<sup>75</sup> The letters to the editor noted the controversy surrounding the study as illuminating "the fragile relationship that could exist between a sponsor and investigators when the results of a study are not as anticipated. The difficult, sobering, and painful lessons learned should be remembered by all when collaborations between industry and academia occur."<sup>76</sup> The study sponsor published an apology in the same issue recognizing that "considering . . . [the] possible commercial impact on our product, we did not place equal weight on . . . academic implication[s] and regret that our decision [to block publication] was interpreted as lack of support for academic freedom."<sup>77</sup>

In 2000 BASF settled a class action lawsuit alleging misrepresentation and unjust enrichment by agreeing to pay \$87.4 million to patient purchasers of Synthroid, \$45.5 million to

third-party payors (insurers and health plans), and \$45 million in payments to states' attorneys general and cy pres remedies.<sup>78</sup> These plaintiff groups alleged that because the manufacturer concealed information about less expensive alternatives in violation of federal and state antitrust laws and consumer fraud statutes, they paid more money for Synthroid than they would have for one of its generic equivalents during the time period that the study was suppressed, and were deprived of the opportunity to save costs by choosing among Synthroid's bioequivalent alternatives.<sup>79</sup> Fortunately, the suppression of important research in the Synthroid episode caused harm only to consumers' pocketbooks, not their health. The Synthroid episode demonstrates the perceived financial benefits and damaging potential of suppressive industry practices.

### **Damage Already Done: Junk Studies and Silicone Breast Implants**

Studies with undisclosed industry funding may have changed the course of litigation against the manufacturers of silicone breast implants. In addition to largely uncontested claims for damages caused by ruptured implants and related damages in the form of explantation, disfigurement, and/or replacement, implant recipients blamed silicone breast implants for other major illnesses, hotly contested by the manufacturers, including connective tissue diseases, such as lupus- and scleroderma-like disorders, characterized by disabling chronic fatigue, aches, pains, fevers and swelling of the joints.<sup>80</sup> Manufacturers Dow Corning, Baxter Healthcare, 3M/McGraw, and Bristol Myers Squibb faced multi-billion dollar litigation on behalf of women with ruptured implants and other illnesses allegedly caused by defective breast implants. Key to many illness claims were studies examining the cause of whether complications experienced by implant recipients was the silicone from the defective implants which had ruptured, leaked, and/or migrated within their bodies.<sup>81</sup>

The same week implant recipients had to participate in or opt out of a \$4.25 billion settlement with Dow Corning, the *New England Journal of Medicine* published a Mayo Clinic study by Dr. S.E. Gabriel et. al., *Risk of Connective-Tissue Diseases and Other Disorders After Breast Implantation*, finding no link between silicone breast implants and a variety of immune disorders in women.<sup>82</sup> The publication of the Mayo Clinic study was not only suspiciously timed but also controversial when it was later reported that industry funding behind the study had been undisclosed.<sup>83</sup>

According to the *Legal Times*, Dow Corning and Bristol-Meyers Squibb Co. contributed over \$700,000 to the Plastic Surgery Education Foundation of the American Society of Plastic and Reconstructive Surgeons (PSEF) which then donated \$174,000 to the Mayo Clinic.<sup>84</sup> The Mayo Clinic credited the PSEF for funding the study without disclosing the corporate funding behind the PSEF. The Mayo Clinic was also criticized for being a major center for implant surgery and a defendant in several cases.<sup>85</sup>

Breast implants plaintiff's attorney Stephen Sheller criticized the methodology of Dr. Gabriel's Mayo study as well as its failure to disclose industry funding. See *Will the Real Junk Science Stand Up? An Analysis of the Mayo Clinic Women's Study and Harvard/Brigham Nurses Study in Relation to the Silicone Gel Breast Implant Controversy*.<sup>86</sup> According to Sheller, the Mayo researchers also did not disclose that initially medical records of 971 women with breast implants received from Mayo were part of the study, but that 149 women were later excluded for not meeting undisclosed criteria.<sup>87</sup> Of those women, 73 who met the criteria were excluded from the published study for undisclosed reasons.<sup>88</sup>

Similarly, Sheller criticized the Harvard Medical School study conducted at the Brigham and Women's Hospital by Jorge Sanchez-Guerrero, M.D. et al., *Silicone Breast Implants and the*

*Risk of Connective Tissue Diseases and Symptoms* in the New England Journal of Medicine, which also found “no link” between breast implants and connective-tissue disease.<sup>89</sup> Both the Mayo Clinic and Harvard studies were epidemiological studies based on the answers to questionnaires mailed to patients, not physical examinations, and did not look for the atypical diseases that are believed to be associated with breast implants.<sup>90</sup> The samples were too small to detect an association with the auto-immune diseases that were included in the questionnaires.<sup>91</sup> The Harvard study purportedly included women who had breast implants for 40.5 years and 37.5 years, but because breast implants were first available in 1962 and the study ended in 1990, the longest any woman could have had her implants was 28 years, thus casting doubt on the accuracy of the data and artificially increasing the average number of years women in the study had their implants. In addition, the Harvard study included women who had had implants for as little as 30 days when the latency period for some of the auto-immune diseases is believed to be 10 to 15 years, and included women with saline implants which are not associated with the health problems of silicone gel implants.<sup>92</sup>

According to Sheller, since 1995 Dow Corning has paid over \$7 million to the Brigham and Women’s Hospital.<sup>93</sup> Dow and other breast implant manufacturers have reportedly paid consulting fees to the study authors and manuscript reviewers, who also served as expert witnesses in litigation on behalf of the manufacturers.<sup>94</sup> The full amount of payments and the nature of the relationships between the authors and industry were not fully disclosed in the literature or to the public. Also, Sheller indicates no discussion was included in the Harvard study of the findings of a larger concurrent but unpublished study at the Brigham and Women’s Hospital in which the researchers found an increased risk of 45-59% of rheumatoid arthritis in

women with breast implants, research that was in direct conflict with the Harvard/Brigham study.<sup>95</sup>

The editor of the New England Journal of Medicine who published both articles, Marcia Angell, MD, had made no secret of her support for silicone breast implants, calling the FDA ban on silicone implants “overly paternalistic” and “unnecessarily alarming” in an editorial in the same issue as the Mayo study.<sup>96</sup> In a later article she criticized lawsuits against silicone breast implant manufacturers, with statements about “a small group of doctors and scientists . . . quick to concoct theories explaining how breast implants affected the immune system without any evidence that they do” and describing the link to systemic diseases as “small, if it exists at all.”<sup>97</sup> Her article described plaintiffs’ evidence against manufacturers as “anecdotal” and public opinion about breast implants as ignorant and bordering on “superstitious.”<sup>98</sup> The timing of the publication of the Mayo study may well have been coincidental; however, her comments as editor and her allegiance to the Mayo study’s findings, despite numerous letters from doctors pointing out its shortcomings, only add to the controversy of its timing.<sup>99</sup>

According to the findings of the Journal of the American Medical Association study, *Press Releases: Translating Research Into News*, press information released to the public about new medical findings do not routinely highlight study limitations, conflicts of interest, or the role of industry funding, and exaggerate the perceived importance of findings. Consistent with such findings, the Harvard and Mayo Clinic studies were largely simplified and exaggerated in the press which claimed the studies showed no evidence of any link between breast implants and autoimmune disease, even touting the studies as evidence of breast implant safety.<sup>100</sup> The influence of the breast implant manufacturers on the studies, the conflicts of interest of the researchers, and the limitations of the studies were largely ignored, as were interpretations of the

data showing that women with implants were twenty-four percent more likely to have a connective-tissue disease.<sup>101</sup> Articles in the news referred to the studies as “independent” and “peer-reviewed,” over-simplified the findings, and ignored major methodological flaws.<sup>102</sup> Breast implant manufacturers ran costly full-page ads in major US newspapers stating that studies at “prestigious medical institutions” such as Harvard and the Mayo Clinic find “no link between breast implants and disease.”<sup>103</sup> Such advertisements misleadingly overstated the actual findings of the studies to a significant degree.

Many of the diseases and injuries widely attributed to implants by implant recipients have still not been adequately studied, despite availability of large amounts of as yet unexplored data from hundreds of thousands of women who participated in the breast implants litigation, and sent voluminous medical records and experts’ reports to the court-appointed Claims Administrator. The FDA is considering lifting the ban on silicone breast implants in 2002.<sup>104</sup> Yet even if silicone has no adverse effects — other than permanently disfiguring women whose implants rupture, leak and/or require explanation (the type of bodily injury the law has long recognized and compensated) — there was an appearance of impropriety during litigation because of non-disclosure of funding sources in studies whose curiously timed release and findings may have changed the course of litigation for some women who claimed harm from their implants. In the judicial forum, non-disclosure and conflicts of interest should be regarded as serious enough to warrant the label “junk” and preclude admissibility.

**Solutions: Universal Guidelines for Scientific Research and  
Closer Judicial Scrutiny of Conflicts of Interest with the Drug Industry**

Leading medical journals increasingly demand that authors who submit manuscripts for publication of the results of studies and clinical trials be responsible for disclosing all financial and personal relationships that may bias their work, and for stating whether potential conflicts do

or do not exist.<sup>105</sup> The International Community of Medical Journal Editors, composed of the editors of the world's most prestigious medical publications, last amended the Uniform Requirements For Manuscripts Submitted to Biomedical Journals Guidelines in 2000.<sup>106</sup> These guidelines include discussion of when researchers should refrain from agreements with study sponsors that limit access to data, independent analysis, or the publishing of manuscripts, and mandate disclosure of any sponsor contribution to study design.<sup>107</sup> For example, the Conflict of Interest section in the Uniform Requirements states:

Public trust in the peer review process and the credibility of published articles depend in part on how well conflict of interest is handled during writing, peer review, and editorial decision making. Bias can often be identified and eliminated by careful attention to the scientific methods and conclusions of the work. Financial relationships and their effects are less easily detected than other conflicts of interest. Participants in peer review and publication should disclose their conflicting interests, and the information should be made available so that others can judge their effects for themselves. Because readers may be less able to detect bias in review articles and editorials than in reports of original research some journals do not accept reviews and editorials from authors with a conflict of interest.<sup>108</sup>

If such guidelines are effective, scholarly independence and academic freedom may yet prevent or combat growing market dominance over research institutions. However, the language of many ethical guidelines is couched in terms of “should” not “will” or “shall” or “must.”

Significant confusion exists among scientists about what conflict of interest exactly means. For example, when the Federal Judicial Center convened panels of court-appointed experts in the breast implant product liability litigation to review studies for admissibility, serious efforts were made to avoid any conflicts of interest. Scientists were initially screened in a telephone call for conflicts of interest. Only when they stated they had none was an application to join the panel submitted to them. The written applications had a series of detailed questions and requirements that very few applicants could actually answer satisfactorily. The pool of qualified applicants turned out to be very small. Many scientists/physicians who orally stated

they had no conflicts of interest actually revealed conflicts only in written conflict disclosure forms.

A June 13, 2002 editorial in the New England Journal of Medicine speaks to the difficulty of publishing information that is free of commercial influence.<sup>109</sup> For review articles and editorials which summarize published articles and synthesize conclusions but do not present new data there was the following policy:

Because the essence of reviews and editorials is selection and interpretation of the literature the Journal expects that authors of such articles **will not have any financial interest** in a company (or its competitor) that makes a product discussed in the article [emphasis added].<sup>110</sup>

After two years of this strict policy the Journal “evaluated the effect on the recruitment of authors and on the range and diversity of our editorials and review articles . . . [and] concluded that [the] ability to provide comprehensive, up-to-date information, especially on recent advances in therapeutics, has been constrained.”<sup>111</sup> In the two years of the implementation of this policy the Journal was only able to solicit and publish one Drug Therapy article on a novel form of treatment.<sup>112</sup> The Journal ceded that if it “publish[ed] nothing on a given subject [it] run[s] no risk of promulgating a biased opinion, but . . . silence does not serve our readers.”<sup>113</sup> Therefore as of June 13, 2001 it modified the policy to read, “the Journal expects that authors of such articles **will not have any significant financial interest** in a company (or its competitor) that makes a product discussed in the article” [emphasis added].<sup>114</sup>

The *de minimis* level for a “significant financial interest” is currently \$10,000 per year.<sup>115</sup> The Journal could not find any authors without financial interests in the products willing to write articles.<sup>116</sup> This policy highlights relationships between researchers and industry, one that the Journal describes succinctly as “growing.”<sup>117</sup>

The requirement of FRE 702 and Daubert that expert testimony be reliable cannot be met if funding sources or other conflicts of interest exist and are concealed. *Daubert*, *Kumho Tire*, and *Joiner* set forth a trial judge's broad discretion to ensure reliable expert testimony. In appropriate instances, the courts should recognize industry dominance in and influence over academia as well as the shortfalls of regulation. Plaintiffs should endeavor to ferret out instances of conflicts of interest, including undisclosed funding, and object to admission of evidence of industry-funded studies in circumstances of non-disclosure, undue influence or scientific bias. A plaintiff-guided focus of judicial scrutiny upon admissibility within the context of non-disclosure and conflicts of interest is necessary to restore balance and integrity to the judicial gate-keeping function.

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<sup>2</sup> Editorial, *Is Academic Medicine for Sale?*, N Engl. J Med., vol. 342, no. 20, 1516 (May 18, 2000).

<sup>3</sup> See Journal of the American Medical Association, vol. 282, no. 17 (Nov. 1, 2000) and New England Journal of Medicine, vol. 343, no. 22 (Nov. 30, 2000). See also New England Journal of Medicine, vol. 324, no. 20 (May 18, 2000).

<sup>4</sup> See New England Journal of Medicine, vol. 345 no. 11 (Sept. 13, 2001), and Journal of the American Medical Association, vol. 287, no. 21 (June 5, 2002).

<sup>5</sup> Editorial, *Sponsorship, Authorship, and Accountability*, N Engl. J Med., vol. 345, no. 11, 825 (Sept. 13, 2001).

<sup>6</sup> *Id.* See also Synthroid case study, *infra*.

<sup>7</sup> *Id.*

<sup>8</sup> Mildred K. Cho, PhD, et al., *Policies on Faculty Conflicts of Interest at U.S. Universities*, JAMA, vol. 284, no. 17, 2203 (Nov. 1, 2000).

<sup>9</sup> *Id.*

<sup>10</sup> *Id.*

<sup>11</sup> Editorial, *Is Academic Medicine for Sale?*, *supra*.

<sup>12</sup> See *id.* and *Madison Avenue Plays Growing Role the Business of Drug Research; Courting Doctors with Food and Cash*, The New York Times, *infra*, and Jerome P. Kassirer, MD, *Financial Indigestion*, JAMA, vol. 284, no. 17, 2156 (Nov. 1, 2000), and David Korn, MD, *Conflicts of Interest in Biomedical Research*, JAMA, vol. 284, no. 17, 2243 (Nov. 1, 2000).

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- <sup>16</sup> *Id.*
- <sup>17</sup> S. Krimsky, et al., *Financial Interests of Authors in Scientific Journals: a Pilot Study of 14 Publications*, Science Eng. Ethics, vol. 2, 395-410 (1996).
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- <sup>19</sup> *Id.*
- <sup>20</sup> *Id.*
- <sup>21</sup> See *Daubert v. Merrell Dow Pharmaceuticals*, 509 U.S. 579 (1993).
- <sup>22</sup> Drummond Rennie, MD, *Fourth International Congress on Peer Review in Biomedical Publication*, JAMA, vol. 287, no. 21, 2759 (June 5, 2002).
- <sup>23</sup> Douglas C. Altman, DSc., *Poor Quality Medical Research, What Can Journals Do?*, JAMA, vol. 287, no. 21, 2767 (June 5, 2002).
- <sup>24</sup> *Id.*
- <sup>25</sup> Kirby P. Lee, MA, et al., *Association of Journal Quality Indicators With Methodological Quality of Clinical Research Articles*, JAMA, vol. 287, no. 21, 2805 (June 5, 2002).
- <sup>26</sup> Melody Petersen, *Madison Avenue Plays Growing Role in the Business of Drug Research: With Billions at Stake, Madison Avenue Guides New Research of Drugs; The Ghostwriter: Articles that Follow Marketer's Advice*, The New York Times (Nov. 22, 2002).
- <sup>27</sup> Steven Woloshin, MD, MS, and Lisa M. Schwartz, MD, MS, *Press Releases: Translating Research Into News*, JAMA, Vol. 287, No. 21, 2856 (June 5, 2002).
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- <sup>30</sup> See Melody Petersen, *Madison Avenue Plays Growing Role in the Business of Drug Research; The Invisible Hand: Courting Doctors with Food and Cash*, The New York Times (Nov. 22, 2002) for President Bush's appointment of the new FDA chief counsel, Daniel E. Troy who fought restrictions on drug promotion as a private lawyer, now leading review of regulations to relax existing limits on behind-the-scenes marketing of drugs.
- <sup>31</sup> Leslie Wayne and Melody Petersen, *A Muscular Lobby Rolls Up Its Sleeves*, The New York Times (Nov. 4, 2001).
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- <sup>35</sup> Lundblad, *supra*.
- <sup>36</sup> Commentary, *Lotronex and the FDA: A Fatal Erosion of Integrity*, The Lancet, vol. 357, 1544 (May 19, 2001).
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- <sup>41</sup> Berger, *supra*.
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- <sup>43</sup> *Daubert v. Merrell Dow Pharmaceuticals*, 509 U.S. 579 (1993), *General Electric Co. v. Joiner*, 522 U.S. 136 (1997), and *Kumho Tire Co. v. Carmichael*, 526 U.S. 137 (1999).
- <sup>44</sup> See *Daubert*, 509 U.S. 579.
- <sup>45</sup> *Frye v. United States*, 293 F. 1013 (D.C. Cir. 1923).
- <sup>46</sup> *Daubert*, 509 U.S. 579.
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- <sup>50</sup> *Id.*
- <sup>51</sup> See *Daubert* at 593-94.
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- <sup>53</sup> Mark R. Patterson, *Article: Conflicts of Interest in Scientific Expert Testimony*, 40 Wm. and Mary L. Rev. 1313 (1999).
- <sup>54</sup> *Id.* at 1316.
- <sup>55</sup> *Kumho Tire Co. v. Carmichael*, 526 U.S. 137 (1999).
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- <sup>57</sup> *Id.* at 141.
- <sup>58</sup> *Id.* at 151.
- <sup>59</sup> *General Electric v. Joiner*, 522 U.S. 136 (1997).
- <sup>60</sup> See *id.* at 147.
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- <sup>69</sup> *Id.* at 9.
- <sup>70</sup> *Id.*
- <sup>71</sup> *Id.*
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- <sup>73</sup> *Id.* at 9.
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- <sup>89</sup> *Id.*
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