

# Registration of Clinical Trials for Pharmaceuticals

By Danielle Bradus

**V**IOXX WAS REMOVED FROM THE MARKET because its use was linked to an increased risk of heart attack and stroke. Paxil may be associated with an increased risk of suicide in children. These are only two examples of many similar stories publicized recently by the media. In light of reports and public disclosure of information, pharmaceutical companies have come under attack for failing to disclose information about the side effects of their drugs. The negative exposure has resulted in numerous lawsuits, an American Medical Association (AMA) study, Congressional Hearings, and a recent ruling by the International Committee of Medical Journal Editors (ICMJE) mandating the registration of clinical trials in a public database before member journals may publish the results of those trials. Pharmaceutical companies have not registered their studies in a timely manner, impacting the scientific community, the medical community, and the public at large. With the recent publicity of problems associated with different medications there is an increased push for the registration of clinical trials. However, registration will have a great impact on the pharmaceutical industry and will not solve all problems related to clinical trials.

## Initial Registration and the Law

TO UNDERSTAND THE EFFECTS OF REGISTRATION and the ICMJE ruling, it is important to have a basic knowledge of the regulation of clinical trials. The Food and Drug Administration (FDA) governs new drug applications and trials under the Food Drug and Cosmetic Act (FDCA). The FDCA originally contained no requirements for the registration of clinical studies. The first proposal for mandatory clinical trial registration arose in the 1970s during President Nixon's "War on Cancer;"<sup>1</sup> however, this push for a registration requirement was unsuccessful.

Congress amended the FDCA in an effort to increase the use of registries. The FDA Modernization Act of 1997 ("Modernization Act") required the registration of clinical trials for serious or life-threatening diseases.<sup>2</sup> The Modernization Act included the following requirements:

A registry of clinical trials (whether federally or privately funded) of experimental treatments for serious or life-threatening diseases and conditions . . . which provides a

description of the purpose of each experimental drug[,] . . . eligibility criteria for participation in the clinical trials, a description of the location of trial sites, and a point of contact for those wanting to enroll in the trial, and shall be in a form readily understood by members of the public.<sup>3</sup>

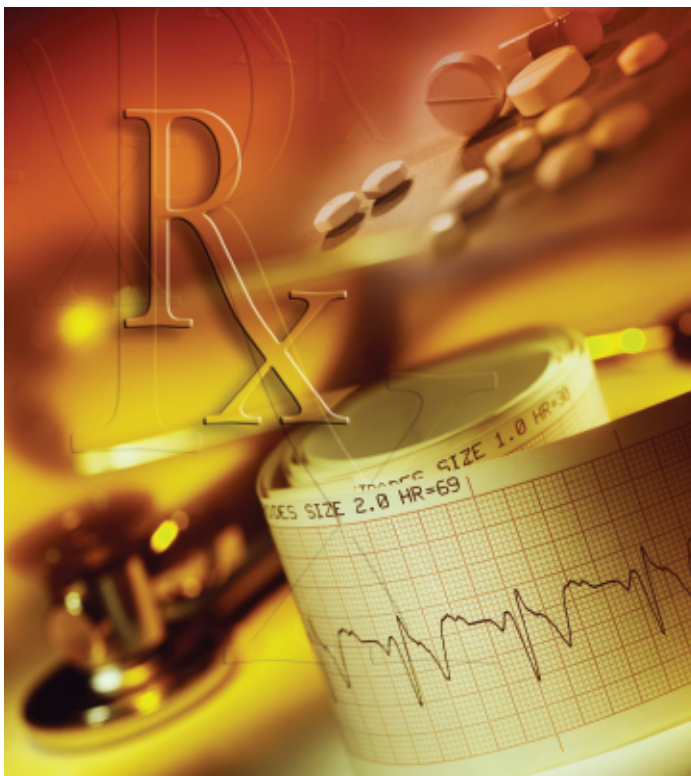
By applying these guidelines to trials involving life-threatening diseases and conditions, the Modernization Act was Congress' attempt to produce a register of trials for the most critical diseases. The Act led the FDA and National Institute of Health (NIH) to create a national register maintained by the United States National Library of Medicine.<sup>4</sup> This registration system became operational in 2000 and contained 10,906 registered trials by June of 2004.<sup>5</sup> Although the register was created for studies involving serious or life-threatening diseases, the database also accepts other listings, such as government-funded clinical trials.<sup>6</sup>

The pharmaceutical industry did not fully comply with the new regulations. From its point of view, the economic cost of compliance, discussed in detail below, outweighed the benefits. Therefore, the Modernization Act did not compel the industry to change its practices drastically. In addition, pharmaceutical companies likely realized that the Modernization Act did not grant the FDA funding or an enforcement mechanism. Therefore, although adhering to FDA regulations might help the industry gain the required FDA approval for new medicines, pharmaceutical companies realized that failure to comply with the mandate was unlikely to result in adverse consequences.<sup>7</sup> The lack of public and media awareness of the benefits and existence of the clinical trial registries may also have contributed to the pharmaceutical companies' failure to comply.<sup>8</sup>

## Awareness Levels

THE LACK OF PUBLIC AWARENESS about the benefits of registration may be due to minimal press coverage about the existence of bias in clinical studies. Without media coverage to alert the public to the possibility that clinical trials are skewed toward a positive outcome, there is no public outcry to change the system. Nevertheless, scientists have known of the lack of registration for years, resulting in large part to problems during the publication of study results. In

fact, for decades, scientists complained about publication bias in medical research, particularly the issue of more frequent reporting of positive results.<sup>9</sup> Publication bias is often attributed to decisions made by the author, investigator, or editor, but may also be present throughout the entire trial, eventually leading to outcome bias.<sup>10</sup> By providing the scientific and medical communities with access to initial information about studies, practitioners may better understand the objectives of each study, the comparative benefits of different study methods, and the markers for success within the studies. This information would help practitioners recognize the impact of various criteria within the published results and enable them to more accurately evaluate the data when deciding whether to use or prescribe a product.



In addition to the publication bias, studies show that an association exists between pharmaceutical industry sponsorship of clinical research and positive results favoring a company's products.<sup>11</sup> This bias, however, may be exacerbated by the fact that many clinical trials are performed to obtain FDA approval, rather than to test new hypotheses or compare efficacy among products.

### Reasons for Selective Registration

AS CLINICAL TRIALS HAVE BECOME MORE SOPHISTICATED, the number of untreated diseases has decreased while the cost of drug development has substantially increased.<sup>12</sup> This cost increase can largely be attributed to the scientific community's attempts to understand and cure more complex diseases - such as Parkin-

son's and Alzheimer's. Today, the average cost of introducing one new drug into the U.S. market is about \$500 million.<sup>13</sup> As a result, pharmaceutical companies running clinical trials actively seek ways to keep costs down.

One method used by pharmaceutical companies to decrease costs is to hire contract research organizations (CROs) to perform trials. CROs are able to perform trials at a lower cost and with fewer hassles than academic researchers. The increased use of CROs has generated competition among CROs and academic researchers which enables pharmaceutical companies to bargain for increased control over all aspects of a study, including trial design, who will have access to the data, and who will have permission to publish the results.<sup>14</sup> With such control, pharmaceutical companies may plan and publish studies focusing on the companies' respective goals without making information available that is in the best interest of patients or scientific advancement.

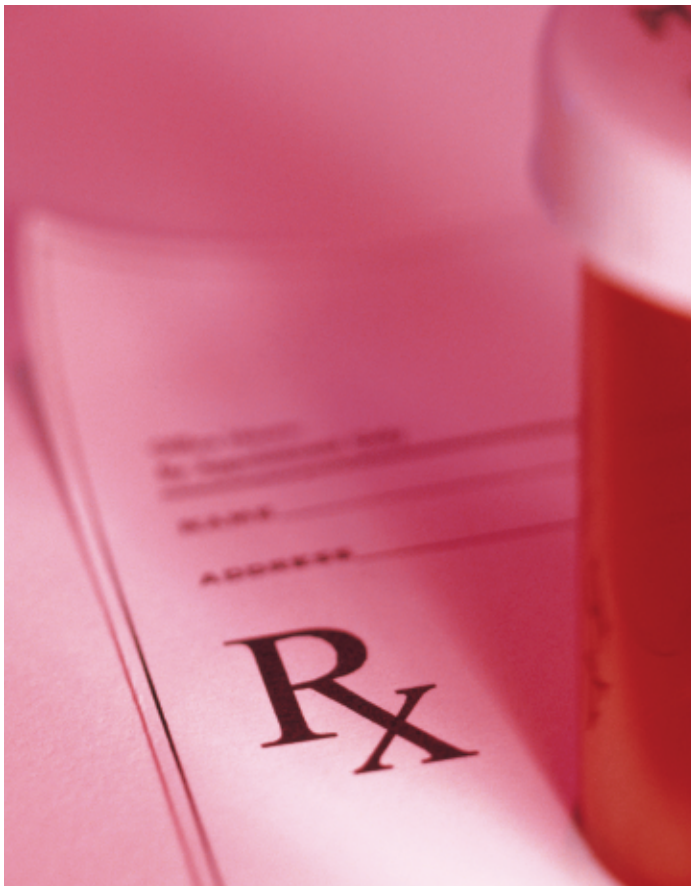
Pharmaceutical companies have much to gain by maintaining complete control over their trials and refusing to register them. Some of the monetary and proprietary benefits include: (1) protection of information about products under development, (2) potential patent acquisitions, (3) concealment of information about recruiting, and (4) avoiding consumer information requests.<sup>15</sup> By keeping studies unregistered, competitors are unable to gain access to information about the drugs involved in the trials.

Failure to register trials often affords pharmaceutical companies with significant financial returns. The recall of Vioxx illustrates how allowing pharmaceutical companies too much control and enabling them to restrict access to pertinent information about a drug may adversely affect consumers. If Merck was aware that Vioxx may cause increased risk of heart attack or stroke,<sup>16</sup> then why did it fail to alert doctors or the public? The answer to this question is simple: the company sponsoring the trial, Merck in this case, often owns the study database and thus may control the release of data,<sup>17</sup> allowing a company to control the publication of information relating to new products. Trials and published study results may be used to market drugs in ways that overstate the drugs' efficacy, producing financial gain for the sponsoring company.<sup>18</sup>

### The Effect of Selective Registration

ALTHOUGH PHARMACEUTICAL COMPANIES have much to gain by taking advantage of selective registration, the consequences of such action within the scientific community and the public are often quite problematic. To uncover the truth about a product the scientific community faces the daunting task of wading through propaganda wasting time and energy that could be used to for medical advancement.

Without full access to information about on-going trials, scientists and medical practitioners are unable to determine what medical research has and has not already been performed. This causes a variety of problems for scientific advancement and patient health. Scientists are limited in their ability to plan future studies when they are unable to build upon current research. Lack of registration may cause the loss or distortion of trial results, waste and duplication of trials, and a chaotic system



from which few pharmaceutical companies benefit.<sup>19</sup> When pharmaceutical companies take advantage of the system for economic benefit, it deters medical advancement and limits the ability of medical professionals to make informed decisions about patient care.

Unfortunately, the public does not learn of the dangers of selective registration until after the harm occurs. In *New York v. GlaxoSmithKline*, the plaintiff alleged that although GlaxoSmithKline (GSK) was aware of the link between use of Paxil by children and suicidal tendencies, this information was withheld from both the medical community and the general public.<sup>20</sup> Unaware of this potentially fatal link, medical professionals continued prescribing the drug to children.<sup>21</sup> As a result of GSK's absolute control over Paxil studies and trials, doctors lacked vital information when they wrote prescriptions for Paxil.

## ICMJE Policy Requirements

IN LIGHT OF CURRENT EVENTS, ICMJE, which includes all the major medical journals, issued a statement that it would not publish the results of unregistered clinical trials. Specifically, the policy requires “as a condition for publication, registration in a public trials registry. Trials must register at or before the onset of patient enrollment.”<sup>22</sup> Additionally, “the registry must be accessible to the public at no charge. It must be open to all prospective registrants and managed by a not-for-profit organization. There must be a mechanism to ensure the validity of the registration data, and the registry should be electronically searchable.”<sup>23</sup>

Currently, <http://www.clinicaltrials.gov> is the only database in existence that meets the ICMJE requirements of (1) a unique identifying number, (2) a statement of purpose of the study, (3) the study's hypothesis, (4) defined primary and secondary outcome measures, (5) eligibility criteria, (6) key trial dates, (7) a target number of subjects, (8) a funding source, and (9) contact information for the principle investigator.<sup>24</sup>

The ICMJE policy forces pharmaceutical companies to act where the law does not. Individual companies must be proactive in registering studies, otherwise, the results will not be published. There is no room for retroactive registration.

## Industry Gains and Losses

With the ongoing wave of negative publicity, the pharmaceutical industry is reacting to the ICMJE policy. Through individual and collective action, the industry has taken steps to ameliorate the harmful impact of past events. For example, the Pharmaceutical Research and Manufacturers Association (PhRMA), the leading pharmaceutical industry group, announced a recommitment to its own programs. Among these programs is a new plan, announced in September of 2004, to create a public database of published and unpublished summaries of clinical trial results.<sup>25</sup>

Individual companies have gone even further to create information transparency. In its settlement with New York Attorney General Eliot Spitzer, GSK agreed to become “the first major drug manufacturer to publicly disclose information on clinical studies of its drugs.”<sup>26</sup> The agreement stipulates that GSK will create an online “Clinical Trials Register” that will contain summaries of all study results for GSK-sponsored studies conducted after December 27, 2000.<sup>27</sup> Other leading pharmaceutical companies reacted to the GSK settlement with their own promises of disclosure. For instance, Forest Laboratories announced a plan similar to GSK's just two weeks after the GSK settlement.<sup>28</sup> Soon after, Merck announced that it will support a government-run register that includes late-stage clinical trials or trials after approval. On August 3, 2004, Eli Lilly

and Company (Eli Lilly) announced a more ambitious program by implementing an independent third party system that verifies Eli Lilly's adherence to its own standards of disclosure.<sup>29</sup>

Despite promises by pharmaceutical companies to disclose clinical trial information, the ICMJE policy is still needed to hold the companies to their word. In the past, companies claimed that they would register their trials, but no permanent, useful, unbiased register resulted.<sup>30</sup> The ICMJE requirement creates an excellent incentive for companies to register. Additionally, under the policy, pharmaceutical companies lose little of their competitive edge in their respective markets since the requirements apply uniformly to all companies. In fact, with the negative publicity surrounding the lack of disclosure, individual companies gain credibility by honoring their word and reporting their trials. If registries and disclosure requirements were in place years ago, as recently as the late 1990s, information about the dangers of drugs such as Vioxx and Paxil would probably have been available to medical professionals and the public. This information may have saved lives.

## Conclusion

WHILE REGISTRATION MAY CAUSE PHARMACEUTICAL companies to lose some control over clinical trials, the medical community would have greater access to clinical trial information, leading to better and safer treatment for patients. Mandatory registration, however, cannot fix all of the problems of selective reporting. Government policy must compel pharmaceutical companies to comply by requiring the registration, monitoring, and enforcement of trials. The ICMJE policy, in addition to the current individual pharmaceutical company policies, presents the best opportunity for improved transparency of clinical trials.

**BLB**

*Danielle Bradus is a second-year JD candidate at American University Washington College of Law. She is a member of the Business Law Brief and the American University Journal of Gender, Social Policy & the Law. Ms. Bradus received her undergraduate degree in Public Policy from Duke University.*

## ENDNOTES: Danielle Bradus

<sup>1</sup> Robert Steinbrook, *Public Registration of Clinical Trials*, 351 N. ENGL. J. MED. 4, 315, 316 (July 22, 2004).

<sup>2</sup> Kay Dickersin and Drummond Rennie, *Registering Clinical Trials*, 290 J.A.M.A. 4, 516, 520 (July 23, 2003).

<sup>3</sup> FDA Modernization Act of 1997, 111 Stat. 2311 § 113(j)(3)(A) (amending section 402 of the Public Health Service Act, 42 U.S.C. § 282).

<sup>4</sup> available at <http://www.clinicaltrials.gov>

<sup>5</sup> Steinbrook, *supra* note 1.

<sup>6</sup> *Id.*; Dickersin, *supra* note 2, at 518.

<sup>7</sup> *Id.* at 520.

<sup>8</sup> *Id.* at 521.

<sup>9</sup> *Id.* at 517.

<sup>10</sup> American Medical Association, *Featured C.S.A. Report: Influence of Funding Source on Outcome, Validity, and Reliability of Pharmaceutical Research 2* (June 2004).

<sup>11</sup> *Id.*

<sup>12</sup> Frank Davidoff, *Sponsorship, Authorship, and Accountability*, 345 N. ENGL. J. MED. 11, 825 (Sept. 13, 2001).

<sup>13</sup> *Id.*

<sup>14</sup> *Id.*

<sup>15</sup> Dickersin, *supra* note 2, at 519.

<sup>16</sup> Marcia Angell, *Merck Downplayed the Risks of its Vioxx*, WALL ST. J., Oct. 7, 2004, at A19.

<sup>17</sup> Steinbrook, *supra* note 1, at 315.

<sup>18</sup> Davidoff, *supra* note 12.

<sup>19</sup> Dickersin, *supra* note 2, at 517.

<sup>20</sup> *New York v. GlaxoSmithKline*, (Compl. at 5-8). Case was settled out of Court.

<sup>21</sup> *Id.* at 4. While Paxil was not specifically approved for children, many states allow medical professionals to expand the use of pharmaceuticals beyond FDA approval based on the physician's professional judgment.

<sup>22</sup> *Clinical Trial Registration: A Statement from the International Committee of Medical Journal Editors*, 292 J.A.M.A. 11, 1363 (Sept. 15, 2004).

<sup>23</sup> *Id.* at 1364.

<sup>24</sup> *Id.*

<sup>25</sup> Press Release, PhRMA, *New Database Provides Doctors and Patients Unprecedented Access to Clinical Study Information for Marketed Medicines* (Sept. 7, 2004).

<sup>26</sup> Press Release, Office of New York Attorney General Eliot Spitzer, *Major Pharmaceutical Firm Concealed Drug Information: GlaxoSmithKline Misled Doctors About the Safety of Drug Used to Treat Depression in Children* (June 2, 2004) (available at [http://www.oag.state.ny.us/press/2004/jun/jun2b\\_04.html](http://www.oag.state.ny.us/press/2004/jun/jun2b_04.html)) (last visited on November 2, 2004).

<sup>27</sup> *Id.*

<sup>28</sup> Press Release, Office of New York Attorney General Eliot Spitzer, *Forest Labs To Establish Clinical Trials Registry* (September 7, 2004) (available at [http://www.oag.state.ny.us/press/2004/sep/sep7b\\_04.html](http://www.oag.state.ny.us/press/2004/sep/sep7b_04.html)) (last visited on November 2, 2004).

<sup>29</sup> Drummond Rennie, *Trial Registration: A Great Idea Switches From Ignored to Irresistible*, 292 J.A.M.A. 11, 1359, 1360 (Sept. 15, 2004).

<sup>30</sup> *Id.*