

# CONFLICTS OF INTEREST IN CORPORATE-SPONSORED ACADEMIC MEDICAL RESEARCH: WHO IS RESPONSIBLE FOR PROTECTING THE PUBLIC?

by

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## I. Introduction

One question especially bothers former *New England Journal of Medicine* editor, Dr. Marcia Angell: Is academic medicine for sale?<sup>1</sup> A recent trend in the field of academic medicine, particularly university research, has Dr. Angell and countless other experts troubled. Over the past twenty years, close relationships have developed between university researchers and the pharmaceutical and biotechnology industries. Financial arrangements between researchers and industry have become the norm, with financial incentives offered to physicians for their support of a particular company or product. These incentives range from small, seemingly insignificant gifts to larger financial rewards such as equity interests, royalty payments or consulting fees from companies whose products they research.<sup>2</sup> The concern is that physicians and researchers who have financial ties to corporations supporting their research can be influenced professionally by their potential rewards. With such incentives in place, Dr. Angell and many of her colleagues are concerned that the outcome of academic research will be based on financial gain, not scientific objectivity.<sup>3</sup>

The conflicts of interest that are associated with corporate sponsorship of academic research have become the subject of much discussion within the academic medical community. A two-day conference at the National Institute of Health (“NIH”) in August, 2000, entitled “The Human Subject Protection and Financial Conflicts of Interest Conference” brought together researchers, ethicists, government regulators, and other interested parties to discuss current trends in academic research and some of the problems that academic-industry relationships have caused. The main objective of the conference was to consider new ways to manage conflicts of interest so that research subjects are appropriately informed, and to further ensure that research results are analyzed and presented objectively.<sup>4</sup>

Before attempting to find new ways to manage conflicts of interest for researchers, however, one must first understand the roles and responsibilities of all the stakeholders in a conflict of interest situation—not only the researchers in academia, but also the companies sponsoring the research. This paper addresses the question: when conflicts of interest arise through the corporate sponsorship of academic research, who is responsible for protecting the public?

The paper will define and examine the complex relationships between academic researchers and the pharmaceutical and biotechnology industries and the conflicts of interest that often arise. The costs and benefits of industry support of academia will be weighed, with extensive focus on why these relationships are problematic. The paper will then discuss the guidelines that are currently in place to ensure that scientific integrity is not unduly influenced by financial interests.

After developing a framework for thinking about academic-industry relationships, case study analysis will be used to examine these relationships and their potential problems. The death of an eighteen-year old during a gene therapy trial at the University of Pennsylvania will be used as a case study of corporate-sponsored academic research and the problems that can arise. This case study will examine the various stakeholders involved in close academic-industry relationships: the researcher, the company, the university, the clinical subjects, and the federal regulatory agencies. Specifically, the case study will define the roles each stakeholder played in the University of Pennsylvania situation, and then will analyze the responsibilities of each party, and whether they were fulfilled. Finally, the paper will determine who should be responsible for protecting the public from conflicts of interest, paying particular attention to the responsibilities of the pharmaceutical and biotechnology industries.

## II. Defining Academic-Industry Relationships

The relationships between academic medicine (universities, doctors, and researchers) and industry (pharmaceutical and biotechnology companies) exist in various forms. These forms vary in terms of their potential for financial gain and in their potential to influence professional decision-making. The spectrum of the relationships between the two parties, from least to most influential, is as follows:

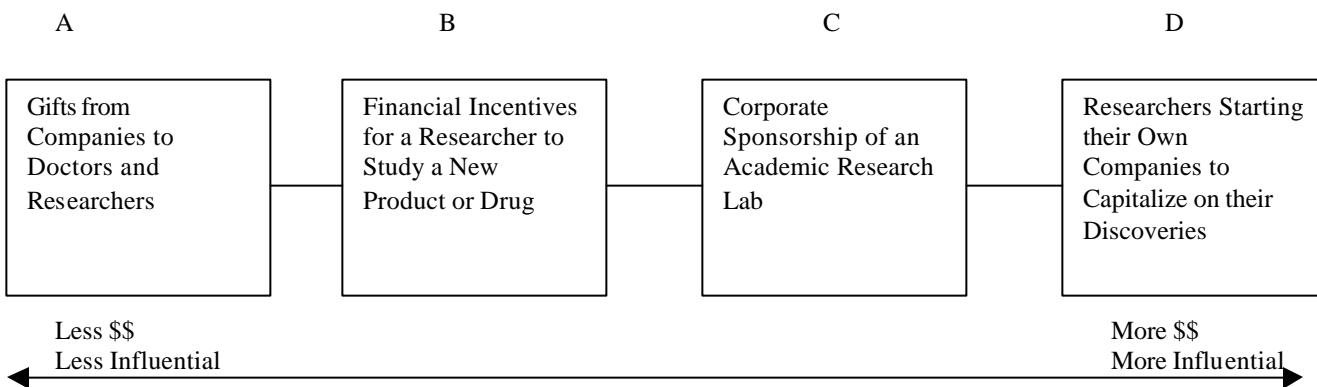
- a) *Pharmaceutical companies offer gifts to doctors who prescribe their drugs to patients.* A common practice among many pharmaceutical companies is to send representatives into hospitals bearing food, supplies, samples of new drugs, and other trinkets for doctors. These gifts are often directed toward medical students and residents with “long prescribing lives ahead of them.”<sup>5</sup> More expensive gifts, including luxurious trips, are also common.<sup>6</sup> These gifts are intended to build and maintain goodwill between physicians and pharmaceutical companies.
- b) *Pharmaceutical companies provide physicians with financial incentives to conduct research and/or publish articles in support of a new drug treatment.* In an effort to obtain approval from the Food and Drug Administration (“FDA”)

for a new drug or treatment, pharmaceutical and biotechnology companies need evidence in the form of research to substantiate the benefits and safety of the product. Companies often enlist academic scientists to perform and publish such research, and in exchange for the researchers' time, effort, and expertise, many companies offer them financial rewards and incentives. Frequently, pharmaceutical companies hire, as consultants to the company, university researchers who are studying the companies' drugs. The scientists who perform the research or write journal articles may receive consulting fees, equity interests, or stock options in the company in exchange for their support of the company and its products. Companies often pay these researchers or "consultants" to publicly promote their products at company-sponsored events.<sup>7</sup> It has also become common practice for a pharmaceutical company to fund an entire university study that involves the company's product,<sup>8</sup> with many of the incentives described above as part of the deal.

- c) *Pharmaceutical or biotechnology companies provide universities with research funds in exchange for exclusive rights to all findings discovered in the university lab.* Universities often contract with a specific company to fund large portions of their entire research endeavor, not just one single study or drug as described above. The companies offer substantial amounts of money to the universities and researchers in exchange for the rights to any important discoveries made in the university lab.<sup>9</sup> These arrangements are often long-term, with a large percent of a lab's annual budget coming from a partner company. When a company takes a university discovery to market, the university and the researchers receive license and royalty fees from the company. In addition to these royalty payments, an equity interest in the partner company for the researcher and the university is often part of the deal.
- d) *University researchers start their own companies to capitalize on their discoveries.* Instead of granting the rights of university discoveries to other for-profit companies as described above, many researchers start their own companies to capitalize on the new drugs and treatments they patent at their university's lab. Researchers start their own companies because of the potential for one of their discoveries to make it to market. Should further research prove that discovery to be effective, the founding researchers are able to develop it for market, reaping financial rewards for themselves and their start-up company. These scientists turned entrepreneurs often work as both university researchers and company CEOs,<sup>10</sup> testing their discoveries through clinical trials and making managerial decisions for the company that will benefit from a successful outcome.

While all of these arrangements involve a close financial relationship between academia and for-profit companies, the variation among these financial arrangements is important. The relationships toward the middle and right side of the spectrum in *Exhibit 1* have the potential to yield significant financial reward for the researchers involved. As the value of the financial reward increases, so does the potential for influence on professional decision-making. Below a certain value, the gain is less likely to play a role.

*Exhibit 1--Spectrum of Academia-Industry Relationships*



Similarly, the arrangements toward the middle and right side of the spectrum are more problematic. Long-term and close associations between academia and industry generate more chance for conflicts to occur.<sup>11</sup> When the relationships are so close that a researcher stands to profit from the outcome of the research, and the profit comes from a company he either has a long-standing relationship with or has founded, the likelihood of influence increases significantly. Most of this document will focus on the right three relationships along the spectrum: pharmaceutical companies providing physicians with financial incentives to conduct research and/or publish articles in support of a new treatment, pharmaceutical or biotechnology companies providing universities with research funds in exchange for exclusive rights to all findings discovered in the university lab, and university researchers starting their own companies to capitalize on their discoveries.

### **III. Background Information**

#### **A. Prevalence of Academic-Industry Relationships**

The area on the left side of relationship spectrum, gifts from pharmaceutical companies to physicians, is extremely common. By one published estimate, drug companies spent an average of \$13,000 on every physician in the United States last year, which adds up to more than \$8 billion. Drug companies employ 70,000 sales representatives, one sales representative for every nine doctors.<sup>12</sup>

The second area on the spectrum, researchers who receive financial compensation to study a company's drug, is also on the rise. In fact, when *The New England Journal of Medicine* ("NEJM") attempted to find an editorialist to publish an article about antidepressant drugs, they experienced difficulty in finding a psychiatrist who had no financial ties to antidepressant manufacturers. The authors of another antidepressant article in the same issue of the *NEJM* had so many ties to drug companies that it would have taken up too much space in the *Journal* to list them all.<sup>13</sup>

Corporate sponsorship of academic research, the third area on the spectrum, is on the rise, growing from \$850 million in 1985 to \$4.25 billion less than a decade later.<sup>14</sup> An article in *The New York Time* notes that "Academic scientists who lack industry ties have become as rare as giant pandas in the wild."<sup>15</sup>

The area on the far right side of the spectrum, researchers forming their own biotechnology companies to capitalize on a university discovery, has been growing particularly fast. Three hundred and sixty-four start-up companies were established in 1998, bringing the total to 2,578 since 1980. It is estimated that these activities generated \$34 billion in 1998 alone.<sup>16</sup>

#### **B. The Origin of Academic-Industry Relationships**

For-profit pharmaceutical and biotechnology companies have large amounts of money at their disposal. Universities, on the other hand, are finding themselves in increasing financial difficulty. Recent reductions in Medicare reimbursements, along with other factors, have left university hospitals and their faculty without the money they need to perform research.<sup>17</sup> When industry helps foot the bill, universities are able to carry out research that they otherwise would not have the funds to support. For these reasons, academia and industry have developed a mutually beneficial partnership.

These university-industry relationships had the chance to grow to new levels, however, with the passage of federal legislation in 1980. The Bayh-Dole Act<sup>18</sup> was enacted by Congress to help move products from university labs to the market place in a timely manner. Before passage of this legislation, the federal government owned the rights to inventions and products discovered through federally funded university research. Any companies wanting the right to develop and/or market these federally supported products or inventions had to go through a lengthy bureaucratic process to obtain a license. However, Congress realized that this process was not the best way to nurture and develop new treatments for market, and that the public could be better served if these innovative ideas were brought into clinical practice without such lengthy delays. The Bayh-Dole Act gave universities and their researchers the right to license patents on findings developed in their labs to companies interested in capitalizing on those findings. "This has allowed the institutions and researchers easier access to money, both for research and for personal profits, and opened up to industry a large market for potential commercial advantage."<sup>19</sup> Today, the Bayh-Dole Act is often invoked to justify close academic-industry ties<sup>20</sup> even if they do not involve the specific patent-licensing agreements the legislation was designed to foster.

### **IV. Benefits Associated with Academic-Industry Relationships**

#### **A. The University**

For academic institutions, relationships with industry offer a number of benefits. Universities are able to generate substantial income from the licensing fees and royalties they receive from companies. Often, based on licensing arrangements, universities enter into close, long-term partnerships with pharmaceutical companies in which students and faculty members study new drugs and treatments that the company hopes to take to market. In exchange for performing the research, companies offer substantial financial support for the university, and many universities rely on funds from these partner companies for a large portion of their research. As described earlier, reductions in Medicare reimbursement and a number of other factors have left some of the most prestigious U.S. universities in growing financial trouble. Deals with companies are one way for academic medical centers to continue to carry out their research.<sup>21</sup>

Another benefit universities reap from their ties to industry is faculty satisfaction. The personal profits these arrangements yield for the researchers give them strong incentive to stay in the university setting.<sup>22</sup> This allows universities to retain their top scientists.

#### **B. The Researcher**

Similarly, researchers benefit greatly from the close industry relationships they cultivate. They have the opportunity to see their discoveries turn into life-saving treatments that help their patients. By working with a company, and benefiting from the financial support it provides, researchers increase the potential for their lab discoveries to actually become marketable.

This arrangement also prevents researchers from having to leave the prestigious academic setting of a university to receive the compensation available to them in industry.<sup>23</sup> In fact, similar to the university institutions they work for, individual researchers often become financially affiliated with a company beyond any patent and royalty arrangements. Many scientists involved in university research have long-standing, personal contracts with specific companies, which can be very lucrative. Common arrangements include consulting fees, equity interests in a company, a seat on a company's board of directors, and a percentage of future sales.<sup>24</sup>

In terms of the drug approval process, there is also potential for researchers to gain financially. When pharmaceutical companies need credible sources to support a new drug, they turn to well-respected academic researchers to back them up through presentations at conferences and publication of journal articles. As described earlier, physicians and researchers are often hired as consultants to pharmaceutical companies, and in exchange for their expertise and support, they receive consulting fees and other rewards described earlier.

### **C. The Company**

The biotechnology and pharmaceutical companies partnering with academic institutions also benefit from their close relationships with academia. By providing financial support, for-profit companies have access to highly respected academic research talent.<sup>25</sup> In fact, it has been documented that companies who partner and publish with leading academic researchers are more likely to succeed than non-partnered companies.<sup>26</sup> Similarly, a strong affiliation with a prestigious university "brand"<sup>27</sup> gives a company increased credibility and authority. Finally, and perhaps most obviously, if a new drug or technique is successfully brought to market, the stock of the company, along with the wealth of its executives, can increase dramatically.

### **D. The Public**

The benefits described for the universities, researchers, and companies together provide significant advantages for the general public in need, or potentially in need, of medical care. Without pharmaceutical money, research and development of new drugs would grind to a halt.<sup>28</sup> With sponsorship from industry, universities have the resources necessary to conduct research they would not have the funds to support on federal grant money alone. These additional resources increase the chances for new treatments and cures to reach the patients who need them. With so much money going into research for cures and treatments of illnesses, our community stands to benefit greatly from breakthroughs that may have never occurred without the extra money industry provides.

## **V. Costs Associated with Academic-Industry Relationships**

Given all of the benefits described above, why is the significant trend toward corporate sponsorship of research problematic? There is concern among many interested parties that a close relationship between universities and for-profit companies threatens the objectivity, independence and openness of academic research. Traditionally, there has been very little overlap in the goals of academia and for-profit business. One strives for knowledge and truth, the other for financial success.<sup>29</sup> When these two missions are interwoven, the question becomes: Does the goal of profit blur the goal of knowledge and truth? Can these two fundamentally different motivations co-exist? The concern is that close academic-industry relationships will bring these two very different goals so close together that they become indistinguishable to universities and their researchers. If there is potential to gain financially from the outcome of their research, there is strong incentive for the goal of profit to weigh more heavily on research decisions than the goal of knowledge and truth.

### **A. Conflicts of Interest**

When academic pursuits come into conflict with financial pursuits, the researcher is in a situation called a conflict of interest.<sup>30</sup> Generally, a conflict of interest is a situation in which professional judgment regarding a primary interest tends to be unduly influenced by a secondary interest. Primary interests are the fundamental professional responsibilities of the person involved. Two relevant examples of primary interests include a patient's welfare and the validity of research findings. Secondary interests are the avoidable influences that have the potential to shift focus away from the priority primary interest.<sup>31</sup>

While secondary interests can come in different forms, such as financial gain, personal prestige and power, or the support or continuation of previous research findings, they are not, in and of themselves, illegitimate or harmful. These interests can be beneficial and necessary. Academic researchers, as much as other professionals, deserve financial and personal

recognition for their contributions to society. In fact, without secondary interests, some valuable scientific research may never have the chance to be applied outside the laboratory,<sup>32</sup> or even to be conducted in the first place. Secondary interests become problematic only in relation to the weight given to the primary interest in professional decision-making. It is only when objectivity, integrity, and honesty, three crucial primary interests of academic researchers, are compromised in pursuit of a secondary interest that problems arise.<sup>33</sup>

Conflicts of interest in corporate-funded academic research require different analyses than other ethical dilemmas commonly discussed in the medical field. For example, euthanasia, the practice of mercifully ending a terminally ill person's life to prevent intolerable suffering and/or undignified death,<sup>34</sup> raises an ethical issue quite different from the conflict of interest dilemma discussed here. With euthanasia, the issue does not involve a primary versus a secondary interest. In an ethical dilemma such as euthanasia, both sides can be understood to have priority over the other, depending on the position of an individual. There is a choice to be made regarding which side should prevail. In a conflict of interest dilemma, clearly the primary interest has priority, and the dilemma is how to avoid undue burden of the secondary interest, not which interest is more important. To analyze financial conflicts of interest the same way as other ethical choices between competing values is to "dilute the concept of a conflict of interest and encourage the attitude that conflicts are so pervasive that they cannot be avoided."<sup>35</sup>

When conflict of interest issues arise, the medical community is often appalled at the notion that it could possibly be capable of placing financial rewards over the safety of patients or the integrity of research. The problem is not that researchers are consciously choosing their own fiscal reward over scientific integrity. However, when the goals of scientific research are interwoven with the goals of profit, there is evidence to suggest that the secondary interest can affect professional decision-making.

## **B. Evidence of Problems**

### **1. Industry Incentives for Drug Research and Publication**

One area of research where conflicts of interest have been extensively documented is the approval or support of new drugs by researchers with pharmaceutical company ties, the second area of the relationship spectrum described earlier. A number of studies have been performed in an attempt to understand and quantify the extent to which pharmaceutical industry support of research influences the opinions and behavior of clinicians and researchers. For example, in a recent *New England Journal of Medicine* study entitled "Conflicts of Interest in the Debate over Calcium-Channel Antagonists," it was found that physicians and medical scientists who accept money from pharmaceutical companies have a higher propensity to support new, controversial drugs than their colleagues who do not accept funding arrangements. This study was conducted in reference to calcium-channel antagonists, which is a controversial high-blood pressure drug whose safety had been under question because of concerns that it increases the risk of heart attack death.<sup>36</sup>

The study examined seventy articles on the calcium-channel antagonist safety controversy. Articles were classified in one of three ways: supportive of the drug, neutral, or critical of the drug's safety. The authors of each article received surveys asking about their financial relationships with manufacturers of calcium-channel antagonists, as well as with manufacturers of competing products. The funding could have been in the form of funds for travel expenses, honorariums for speeches, support for educational programs, research grants or employment or consulting compensation. Eighty percent of authors contacted responded to the questionnaire, resulting in a sample size of seventy articles for analysis.

The authors of the *NEJM* study concluded that there is "a strong association between the author's published positions on the safety of calcium-channel antagonists and their financial relationships with pharmaceutical manufacturers." Ninety-six percent of authors whose articles supported the use of the drug had received funding from a manufacturing company. This was in contrast to sixty percent of authors who had a neutral stance toward the drug, and thirty-seven percent of authors who were classified as critical of the drug's safety. Similarly, one-hundred percent of supportive authors were considerably more likely to have financial relationships with pharmaceutical companies in general, regardless of the drug, compared with sixty-seven percent of neutral and forty-three percent of critical authors.<sup>37</sup>

"The influence of pharmaceutical funding on the medical profession and on the drug approval process is very widespread and dangerous," says Dr. Michele Brill-Edwards, former senior drug evaluator for Health Canada and co-director of the Alliance for Public Accountability in Ottawa.<sup>38</sup> The concern is that increasing reliance on pharmaceutical funding and compensation encourages university researchers to overstate the benefits of new treatments, and minimize the potential risks.<sup>39</sup> If this continues, the public will no longer be able to trust the work done by medical professionals who have the chance to gain financially from the outcome of that work. Dr. Brill-Edwards continues, "Millions of dollars and countless lives are lost when drug risks are downplayed by researchers with drug-company ties."<sup>40</sup>

Perhaps an even more frightening scenario than a scientist downplaying or not reporting side effects of new drugs occurs when company sponsors delete or change researchers' findings in an effort to keep bad news from publication. In the summer of 1996, four researchers studying the same controversial high blood pressure treatment described in the *NEJM* study--calcium channel antagonists--quit in protest after their sponsor, Sandoz, removed passages from a manuscript highlighting the drugs' potential dangers. In a letter to the *Journal of the American Medical Association*, the researchers

stated that, "We believed that the sponsor ... was attempting to wield undue influence on the nature of the final paper. This effort was so oppressive that we felt it inhibited academic freedom."<sup>41</sup>

It has become common practice for the pharmaceutical companies, not the scientists who performed the research, to have the final say on what is published about a product. In a number of instances like the one described above, there is evidence of companies suppressing or attempting to suppress publication of research findings that may be damaging<sup>42</sup> to the drug's potential for market, and thus the company's bottom line. "Companies want a final say...and more researchers are accepting," says Nikki Zapol, director of corporate-sponsored research at Massachusetts General Hospital. More than half of all industry contracts have clauses allowing companies to suppress research findings.<sup>43</sup>

## 2. Arrangements Between Universities and Industry

When entire university departments accept funding from industry in exchange for the rights to all discoveries made at the university, intense conflict of interest issues arise. A recent deal between the University of California and a Swiss pharmaceutical company is raising eyebrows. Novartis, formerly known as Sandoz (the company criticized for suppressing researchers' negative findings), will pay the University of California \$25 million in exchange for the rights to any discoveries made in the university's plant genetics lab.<sup>44</sup> The deal also grants Novartis significant power over how the \$25 million is spent by allocating two out of five seats on the department's research committee to the company.<sup>45</sup>

One concern with this type of university-industry partnership involves the nature of research the university and scientists will choose to, or be permitted to, conduct. The corporate sponsor is eager for the university and its researchers to become involved with projects that have an immediate application and immediate commercial potential, more so than other, more scientifically significant research.<sup>46</sup> Similarly, the researchers involved will be more eager to participate in this marketable research for the potential financial gains they can achieve in terms of stock value they may hold in the company. The problem is that more research will be conducted on immediately marketable products including new drugs and techniques to treat a disease, and less on the causes and workings of the disease itself,<sup>47</sup> which can have more of a long-term impact.

The concern most often expressed in terms of these arrangements, however, involves the financial rewards offered to researchers by the industry partner. If researchers have the potential to gain from the outcome of their research, either in terms of stock value that they hold in the company or license fees from a patent they hold, the potential for influence over professional decision-making is significant. When considerable personal wealth is the direct result of a specific research outcome, the desire for that outcome can be so great that professional judgment has more to do with achieving the desired results than with scientific accuracy. And it is not difficult to understand how these arrangements can subtly influence scientific objectivity. Dr. Angell asks the question, "Can we really believe that clinical researchers are more immune to self-interest than other people?"<sup>48</sup> Dr. Brill-Edwards of the Alliance for Public Accountability agrees: "My 15 years as an expert in drug evaluation told me that many researchers seem blind to the important role company money can play in their thinking about drugs." She continues, "Doctors funded by industry are like captains of the Titanic: they come to think their judgment is unsinkable and this puts public safety at risk...whether they know it or not, doctors' judgments are being influenced in a very big way."<sup>49</sup>

## 3. University Researchers Starting Their Own Companies

The relatively new phenomenon of researchers starting their own companies to capitalize on their university research has raised new conflict of interest concerns. As described earlier, the passage of the Bayh-Dole Act<sup>50</sup> made it legal for universities to patent products and techniques developed in their labs, and license the rights to those products and techniques to for-profit companies. An article in *The New York Times* entitled "Biomedicine Is Receiving New Scrutiny as Scientists Become Entrepreneurs"<sup>51</sup> describes a number of situations in which university researchers started their own biotechnology companies to develop and capitalize on the products and therapies they discovered, instead of licensing that right to another company.

Dr. William Haseltine, a former professor at Harvard University, founded seven biotechnology companies while still working for Harvard. "I don't even know how many millions I've made," Dr. Haseltine commented to *The New York Times*. He now acts as chief executive officer of Human Genome Sciences, one of the seven biotechnology companies he started to develop gene therapy techniques. Dr. Haseltine continues, "The motivation was not primarily money. The motivation was the joy of conceiving ideas and reducing them to practical reality to make a difference in people's lives."<sup>52</sup>

One field of science where a significant number of doctors, including Dr. Haseltine, have started their own biotechnology companies is gene therapy, a new technique that involves treating the damaged cells of patients with healthy, corrective genes. The American Society of Gene Therapy states that gene therapy has tremendous potential to positively shape future therapies for a variety of conditions including inherited disorders, cancer, heart disease, neurological disorders, AIDS and other infectious diseases.<sup>53</sup> However, the true capabilities of gene therapy remain to be seen, as many gene therapy trials have not been as successful as hoped.

The potential for financial conflicts of interest in gene therapy research is of particular concern because testing most often takes place in clinical trials where gene therapy treatments are given to human subjects. And when the doctor or scientist

performing human experimentation also runs or owns the company that will profit from its success, the potential for conflicting interests is high. The fear is that doctors who enroll and treat patients in clinical studies that are paid for by the companies they own may withhold information about potentially dangerous side effects, in fear that the information could hurt investments in their companies or delay approval by the FDA. Another concern is that doctors who own the companies that fund their research may push for experiments that may not be ready for clinical trial out of eagerness to move the product to market. Dr. David Blumenthal, director of the Institute for Health Policy at Massachusetts General Hospital, states that conflicts of interest are “particularly difficult to justify in cases where patient’s welfare may be affected.” According to the FDA, the practice of doctors recruiting patients into clinical trials sponsored by their own companies is growing in gene therapy.<sup>54</sup>

A number of university researchers who started their own gene therapy companies have come to the attention of the National Institute of Health (“NIH”) for many of these reasons. Dr. Ronald G. Crystal of Cornell’s Medical School founded his own gene therapy company, Gen-Vec, which sponsored some of his clinical trials. The Recombinant DNA Advisory Committee (“RAC”), the panel that oversees gene therapy research for the NIH, criticized Dr. Crystal for asking the panel not to disclose that one of his patients had died of an underlying illness during a clinical trial. Further research enabled the NIH to learn that most gene therapy researchers were not complying with its reporting guidelines.<sup>55</sup> In fact, out of 691 adverse events related to gene therapy, 652, or ninety-four percent, were not reported as required by the NIH. Adverse events include patient allergies, drug interactions, dosing errors, side effects, or any other unforeseen reactions to the trial. The effects can range from a mild allergic reaction, to stomach ulcers, elevated blood pressure or even death. These adverse events that the NIH requires to be reported “are viewed by business as driving down the price of stock and helping competitors avoid mistakes.”<sup>56</sup>

“More and more, clinical investigation in gene therapy is being done by those with equity interests, severely stressing their judgment,” said Alan Schechter of the NIH in regards to conflicts of interest when gene therapy researchers start their own companies. “Gene therapy has many of the worst examples of clinical research that exist.” The NIH also provides statistics that support these statements. Of the 372 human gene-therapy trials registered with the RAC, 215 are paid for solely by industry and conducted by academic university researchers. Of the remaining 157 trials funded in part by the NIH, many receive industry money in addition to the NIH grants.<sup>57</sup>

### C. Case Study Background

The incident that has raised the most awareness of these conflict of interest issues occurred at The University of Pennsylvania’s Institute for Human Gene Therapy (“IHGT”), where an eighteen-year-old died in a gene therapy clinical trial September 17, 1999. This case involves the three forms of academic-industry relationships: a company paying academic researchers to study a new treatment, a company-university long-term funding arrangement, and a researcher who began his own biotechnology company to capitalize on his university findings. The University of Pennsylvania and its head gene therapy researcher, Dr. James Wilson, had close financial arrangements with Genovo Inc, a biotechnology company founded by Dr. Wilson, that contributed one-fifth of IHGT’s annual \$25 million budget. Both Wilson and the University of Pennsylvania had large equity stakes in Genovo, the company that, in turn, had exclusive rights to develop and market everything discovered at the lab.<sup>58</sup> The case will be discussed in greater detail in Part VII.

## VI. Current Management of Conflicts of Interest

With all of the problems associated with conflicts of interest in corporate-sponsored academic medicine, clear regulatory guidelines are necessary. However, despite the recent scrutiny of academia-industry relationships, few federal regulations are currently in place.<sup>59</sup> Generally, there are three strategies for managing conflicts of interest: disclosure, review and authorization, and prohibition. Which strategy is most appropriate depends on the type of conflict and the potential for real or perceived harm.<sup>60</sup>

**Disclosure.** Disclosure, the remedy most commonly prescribed to deal with conflicts of interest,<sup>61</sup> requires a researcher, author, or speaker to reveal any financial affiliations with a corporate sponsor. While trust may be eroded if patients and others are aware of financial interests though disclosure, a higher level of trust is likely to develop if the physician or researcher is honest and open about financial interests.<sup>62</sup> Disclosure provides those who may be affected by the risks associated with financial interests the information they need to make their own decisions.<sup>63</sup>

**Review and Authorization.** Institutions often establish formal review systems to monitor the conflicts of interest of their researchers. Institutional Review Boards, or IRBs, are designed to determine whether conflicts of interest are affecting, or have the potential to affect, the proper conduct of research. An IRB is also responsible for ensuring that proposed research complies with the federal government's regulations to protect human subjects in research.<sup>64</sup>

**Prohibition.** The final strategy in managing conflicts of interest is to simply not allow them to exist. If a financial arrangement is deemed too problematic, it may be prohibited altogether, or physicians or researchers would have to withdraw completely from any work in which they have a prohibited secondary interest.<sup>65</sup>

These three strategies for conflict of interest management have been put into practice in varying ways. However, current conflict of interest policies are highly inconsistent from university to university. Federal Policy developed by the Public Health Service (“PHS”) in 1995, “Policy for Promoting Objectivity in Research,” leaves the responsibility for conflict management and regulation to each individual university.<sup>66</sup> The PHS Federal Policy is as follows:

Institutions receiving research money from the Public Health Service (PHS) must maintain and enforce a written conflict of interest policy and take steps to prevent scientific misconduct. An awardee institution must have a policy for investigating and acting on suspected or alleged misconduct. In certain situations the PHS must be immediately notified of the apparent misconduct. The conflict of interest policy must identify, evaluate and resolve conflicts of interest, and if they cannot be resolved, report them to the PHS. Financial disclosures must be updated annually. Records of same must be kept for three years after the expiration of an award or grant (42 C.F.R. §§ 6.04 and 6.05). The regulations on conflict of interest define and set standards for the management of financial interest that will, or may reasonably be expected to, bias a clinical research project, the evaluation of the safety or effectiveness of a drug, or a medical treatment or device. In addition, all research involving human subjects requires the establishment of an Institutional Review Board.<sup>67</sup>

It is important to note that the disclosure guidelines described by the PHS are only applicable if a university researcher receives grants from the federal government, either exclusively or in addition to industry money. Faculty members with financial interests in industry-sponsored research without federal grant money are not necessarily bound by these regulations to disclose their conflicts. As such, researchers with the highest potential for conflicting interests, those with significant industry ties, may be excluded from the PHS regulation.<sup>68</sup>

While specific researchers who do not receive federal grant money are not bound by the PHS disclosure regulations, if their home university receives any federal funding, that university is required to have a system for managing faculty conflicts of interest. It is then at the university’s discretion how to handle a researcher with strong industry ties.

The PHS regulations described above have led to wide variations among conflict of interest policies at U.S. universities. A study performed by *The Journal of the American Medical Association* (“JAMA”) examined the policies of the 100 U.S. institutions with the most funding from the National Institute of Health in 1998. Eighty-nine policies, or ninety-two percent, were available and included in the analysis.<sup>69</sup>

The results of the JAMA study showed wide content variation among the sample policies. In terms of disclosure, fifty-five percent of the policies required disclosure from all faculty, with the remaining forty-five percent requiring disclosure only from the faculty performing the research or serving as principal investigator. Eighty-eight percent of the policies surveyed required disclosure of faculty family member’s financial interests. Seventy percent of the policies required disclosure of financial interests in all professional activities, with twenty-seven percent requiring disclosure of only research-based interests. Only two out of the eighty-nine institutions required disclosure of all financial interests.<sup>70</sup>

The authors also searched the sample policies for specific prohibited activities with regard to research and teaching. Nineteen percent named specific activities that were not permitted, including faculty having a financial interest in a company sponsoring their research. The remaining eighty-one percent of policies did not prohibit any specific arrangements.<sup>71</sup>

## **VII. Case Study**

The death of Jesse Gelsinger has led to increased scrutiny of conflicts of interest in biomedical research, particularly the emerging field of gene therapy. Jesse’s death was the first fatality linked directly to gene therapy treatment,<sup>72</sup> and there are now numerous questions about the role financial conflicts of interest played in Jesse’s death, as well as the role financial conflicts of interest play in professional decision making in general. This case study will first examine the roles of each stakeholder in the case. Second, the case study will analyze the legal and ethical responsibilities of each stakeholder, and whether they were fulfilled.

### **A. Stakeholder Roles**

#### **1. Dr. James Wilson**

Dr. James Wilson is considered a first-class researcher<sup>73</sup> and leading geneticist<sup>74</sup> by all who know him and his work. Specifically, he has a reputation for excellence in the emerging field of gene therapy.<sup>75</sup> Dr. Wilson has been successful, not only in academic research settings such as the University of Michigan and the University of Pennsylvania (“Penn”), but also in entrepreneurial ventures designed to capitalize on his research findings.

While working for the University of Michigan, Dr. Wilson patented a half dozen gene therapy related products or techniques.<sup>76</sup> In an effort to capitalize on his patents, Wilson started his own biotechnology company, Genovo, Inc., in 1992.



A number of Dr. Wilson's patents, in particular, seemed to have substantial potential because they involved the use of a gene transfer methodology called the RDAd vector, or the replication-defective adeno-viral vector, the one used on Jesse Gelsinger.<sup>77</sup> RDAd involves the use of adenoviruses, a class of viruses that are extremely efficient at infecting human cells. As such, adenoviruses have proven an efficient means for transferring healthy genes to defective cells in gene therapy treatments. However, they can also trigger intense immune-system responses, and thus can cause patients to experience severe reactions. To combat this problem and still use the RDAd vectors as a means of gene transfer, Dr. Wilson developed a less inflammatory adenovirus by deleting different combinations of the virus' genes so that they could be safe enough to use in the high dose requirements for effectiveness in gene transfer.<sup>78</sup> Dr. Wilson's company, Genovo, would benefit should the modified RDAd vector prove to be an effective method to transfer genes into humans, in that Genovo would have the right to market and capitalize on all future applications.

In 1993, Dr. Wilson was recruited from the University of Michigan to the University of Pennsylvania.<sup>79</sup> The dean of Penn's Medical School, Dr. William Kelley, recruited Dr. Wilson as Director of the Institute for Human Gene Therapy ("IHGT"). Dr. Kelley was also a patent holder of a gene therapy technique that involved the use of the same RDAd vector. His patent enabled him to collect royalties should gene therapy research using the vector prove to be effective through further research, similar to Dr. Wilson's situation with his patents. Dr. Kelley was the person who approved the clinical trial that would eventually kill Jesse Gelsinger, one of the trials that used the RDAd vectors to transfer healthy genes to patients. "Dr. Kelley, Genovo, and Dr. Wilson all stood to gain financially from the successful use of RDAd vectors."<sup>80</sup>

By early 1995, Dr. Wilson had obtained \$36 million in corporate funding for Genovo, most of which came from Biogen, Inc, a large, successful biotechnology company. At the same time, the university began discussions with Dr. Wilson pertaining to an arrangement between the University and Genovo.<sup>81</sup> The agreement provided the university with \$21 million in funding from Genovo, nearly one-fourth of IHGT's five-year budget, in exchange for exclusive rights to license patents discovered at IHGT, which were granted to Genovo, Biogen, and the other corporate sponsors through the year 2000. The arrangement also allowed Dr. Wilson to own 30% of Genovo's stock. At the time of Jesse's death, Dr. Wilson held over twenty patents related to gene therapy, with others pending<sup>82</sup>. Also at the time of Jesse's death, Dr. Wilson was acting as "an agent, servant, representative and employee of the University" of Pennsylvania, as well as "an agent, servant, workman, and employee of Genovo."<sup>83</sup>

## **2. Genovo, Inc. and its Corporate Sponsors**

As previously mentioned, Genovo, Inc. was founded by Dr. James Wilson in 1992. As described by the Biotechnology Industry Organization, of which Genovo is a member, Genovo is

a privately held biotechnology company focused on the design, manufacture and clinical development of gene based therapeutic products for the treatment of human disease. Genovo's innovation in gene delivery using viral vectors for the administration of therapeutic proteins has garnered industry validation and investment. In 1995, Genovo achieved an early important milestone by entering into a strategic corporate partnership with Biogen, Inc. to develop and commercialize gene-based therapies for lung and liver diseases...<sup>84</sup>

Genovo's deal with Biogen, negotiated by Dr. Wilson, allowed Genovo to receive funds from Biogen, yet operate independently from the company's influence. Wilson chose Biogen as a corporate partner because of its position toward his research, which was not to interfere with the day-to-day operations of his company. Kathryn Bloom, a Biogen spokesperson, stated that Genovo's arm's length relationship with its investors was designed to enable Wilson to move at his own pace. And while Biogen had two representatives on Genovo's Board, they did not participate in the day-to-day activities of the company, or the work it sponsored at Penn's IHGT.<sup>85</sup>

The Genovo arrangement with the University of Pennsylvania provided the IHGT with over four million dollars annually from 1995 through 2000. In exchange for Genovo's substantial financial support of Penn's genetic research and experimentation, the University granted Genovo licenses for all lung and liver applications developed by Dr. Wilson in the lab. These licenses would allow for full patent reimbursement, milestone payments and royalty payments on product sales. The university was given 5% equity control of Genovo through the agreement.<sup>86</sup> According to 1996 Penn board minutes, Penn had rights to as much as 15% of Genovo stock.<sup>87</sup> At all times, Dr. Wilson controlled up to 30% of Genovo's stock. Other shareholders of Genovo included other past and present Penn employees, and the other founders of Genovo.<sup>88</sup>

## **3. The University of Pennsylvania**

When the University of Pennsylvania first discussed with Dr. Wilson an arrangement with Genovo, the University's Conflicts of Interest Standing Committee ("CISC") held meetings to consider the implications of such a deal. At a meeting of the CISC in February, 1995, faculty members listed their concerns regarding a close relationship between the University, Genovo, and Dr. Wilson.<sup>89</sup> According to the minutes of the meeting, concerns regarding conflicts of interest were expressed

in the following way: “Since Dr. Wilson’s research efforts will be directed toward the solution of a problem in which he has an interest in the outcome, how can Dr. Wilson assure the University that he will not be conflicted when making decisions that could have an impact on either Genovo, Biogen, or the further development of his intellectual property?”<sup>90</sup>

The CISC clearly expressed its conflict of interest concerns should Dr. Wilson be permitted “to conduct experiments at IHGT which, if successful, would directly benefit Dr. Wilson and Genovo financially.”<sup>91</sup> In an effort to prevent financial conflicts from influencing Dr. Wilson’s research, the university hired a Washington law firm, Hogan and Hartson, as well as a Philadelphia investment bank, Janney Montgomery Scott, to advise them on the situation.<sup>92</sup> The University of Pennsylvania decided to go ahead with the arrangement as previously described. Dr. Wilson would conduct experiments at IHGT as its director, with one-fourth of his annual budget coming from Genovo, of which he had 30% ownership. Penn did, however, establish two different committees to oversee the arrangement. According to Penn’s Vice Provost for Research, Ralph Amado, “the Genovo deal was considered to be sufficiently large in scale, larger than previous undertakings” and therefore, warranted more oversight.<sup>93</sup>

#### **4. Jesse Gelsinger**

Jesse Gelsinger was born with a rare inherited, metabolic disease known as Ornithine Transcarbamylase Deficiency (“OTCD”). OTCD patients are born with a genetic mutation that leaves their liver unable to break down ammonia, a normal byproduct of the metabolic process. High ammonia levels can become fatal. One in forty thousand newborn babies, most of whom are males, are born with a defective OTC gene. One half of all OTC deficient newborns die soon after birth. Jesse was one of the lucky OTCD patients to survive to maturity. His condition remained under control with conventional drugs and diet.<sup>94</sup>

Though Jesse was in relatively good health with his disease under control, he decided to participate in an experimental gene therapy trial for OTCD at the University of Pennsylvania. Jesse would be the eighteenth patient to participate in the Phase 1 Clinical Trial at the University of Pennsylvania’s Institute for Gene Therapy.<sup>95</sup> When he was seventeen years old, Jesse tried to volunteer for the trial. However, the protocol required a patient to be at least eighteen years old. When Jesse turned eighteen, he traveled from his home in Tucson, Arizona to the Philadelphia IHGT to volunteer for the trial. Once accepted into the trial, the research team informed Jesse that the experiment would not cure him of his condition, and that there was even a small chance it could hurt him. Jesse’s decision to participate in the trial was based on “the scientist’s dream that the treatment might someday help severely stricken newborns.” Paul Gelsinger, Jesse’s father, was quoted as saying, “My son had the purest intent. He wanted to help the babies.”<sup>96</sup>

Before going forward with the experiment, Jesse was required to sign an eleven-page patient-consent form. In the final paragraph on the eleventh page of the document, it stated “Please be aware that the University of Pennsylvania, Dr. James M. Wilson (the Director of the Institute for Human Gene Therapy), and Genovo, Inc., (a gene therapy company in which Dr. Wilson holds an interest) have a financial interest in a successful outcome from the research involved in this study.”<sup>97</sup>

On September 13, 1999 Jesse began the gene therapy trial, and thirty milliliters of the RDA vector were injected into his system.<sup>98</sup> The evening of the injection, Jesse was sick to his stomach and had a fever of 104.5 degrees. The morning after the injection, September 14, Jesse was disoriented, jaundiced, and experienced abnormal blood counts. These symptoms were similar to those that had occurred in monkeys injected with a similar vector. The afternoon of September 14, Jesse was in a coma. That night, Jesse’s ammonia level was 393 micro moles per deciliter of blood, with a normal level around 35 micro moles. Jesse was then placed on dialysis. On September 16, Jesse’s kidney’s failed, and he suffered from multiple organ system failure. Jesse was bloated beyond recognition and his eyes and ears had swollen shut. On September 17, Jesse was pronounced dead. The causes of death, acute respiratory distress and multiple organ failure, were a direct result of the injection of the vector.<sup>99</sup>

#### **5. Federal Regulatory Agencies**

The Food and Drug Administration (“FDA”) was responsible for investigating the death of Jesse Gelsinger at the University of Pennsylvania’s Institute for Human Gene Therapy. In a letter to the IHGT, the FDA wrote that they had found “numerous serious deficiencies in the procedures...for the oversight and monitoring” of its clinical trials. The letter noted that such failures would expose subjects to “significant and unreasonable risk.”<sup>100</sup>

The FDA also criticized IHGT for violating specific FDA guidelines. These violations, as listed verbatim in the civil complaint filed by the Gelsinger family, include:

- a. Failing to tell the National Institute of Health Recombinant DNA Advisory Committee (“the RAC”) of a change in the way the virus was to be delivered to patients;
- b. Changing the informed consent form from what had been approved by the FDA by removing information concerning the death or illness of several monkeys during a similar study;
- c. Failing to report to the FDA that patients prior to Jesse suffered significant liver toxicity that required the study to be put on hold;

- d. Failing to follow the study protocol that mandated that in each cohort at least two women be subject to injection before any male;
- e. Admitting Jesse in the trial when his blood ammonia level on the day before he received the gene transfer exceeded the limit set out in the FDA protocol; and
- f. Allowing the vectors to sit and/or be stored on lab shelves for 25 months before being tested in animals, making them less potent than they could have been. The vectors administered to the plaintiff's decedent [Jesse Gelsinger] were only stored for two months. The 25-month storage, in turn, may have resulted in an underestimation of the vector's potency in humans. Additionally, the animals that received the vector stored for 25-months would have been given a dose of vector from 52.2% to 65.3% below the vector dose specified in the FDA protocol.<sup>101</sup>

The FDA also criticized IHGT for mishandling important documentation.<sup>102</sup> According to Phillip Noguchi, Director of Cellular and Gene Therapies at the FDA, "the trial was plagued with poor documentation and...agency officials could find no records that the researchers had noted patients' eligibility for the trial." He continued, "Half the consent forms were not properly filled out" and the FDA "had concerns that the Institute...was not able to comply with the regulations."<sup>103</sup> In total, the FDA found eighteen potential violations by the IHGT.<sup>104</sup>

After investigating the death of Jesse Gelsinger, and the practices of IHGT in general, the FDA suspended all seven of the Institute's clinical trials, five of which had already enrolled patients, on January 21, 2000.<sup>105</sup> The FDA then required Penn's IHGT to respond to all violations found during their investigation, and for the IHGT to provide a detailed plan for the monitoring and oversight of each of the halted clinical trials. Where deficiencies were found, the IHGT was responsible for reporting to the FDA what had been done to rectify the situation.<sup>106</sup>

## **B. Stakeholder Responsibilities**

The death of Jesse Gelsinger brought a wave of scrutiny on clinical trials performed by researchers who stand to gain financially from their research. Clearly, something went wrong during Jesse's clinical trial. The question of whether financial interests played a role in any of the problems is almost impossible to answer. However, with such a close, lucrative relationship between the University of Pennsylvania, Genovo, and Dr. Wilson, it is also impossible to say that financial interests did not play a role. We will now examine the responsibilities of each stakeholder, and whether they were fulfilled.

### **1. Dr. James Wilson**

Dr. Wilson's intimate ties with both Genovo and the University of Pennsylvania created a complicated situation. As both founder and part owner of Genovo, and researcher, professor and physician at the University of Pennsylvania, his motivations were inherently in conflict. Add to the mix that he held several patents that would be of tremendous value should they prove to have commercial applications, and the situation becomes even more complex. However, even after reviewing the financial arrangements in this situation, it is impossible to say that financial interests definitely did play a role in Dr. Wilson's professional decision-making regarding his research. "It is almost impossible to find a smoking gun," said Mildred Cho, a bioethicist at Stanford University with regard to the function Dr. Wilson's commercial ties played in Gelsinger's death.<sup>107</sup>

While it is difficult to know whether conflicts of interest influenced Dr. Wilson professionally, there are a number of questions that arose after Jesse's death that remain unanswered. For instance, with such a close, intimate relationship between Genovo, Dr. Wilson, and IHGT, and so much to gain financially for the three parties, why would a disclosure of the relationship be buried in the last paragraph on the last page of the consent form, unless it was deliberately being downplayed or avoided? If the three parties were confident that the arrangement was well managed and not problematic for the patient's safety, why bury it so far into the document and, more importantly, why not discuss it openly with Jesse and his family? It was the responsibility of Dr. Wilson to place his primary interests, the integrity of his research findings and the safety of his patients, above any personal financial interest, and part of that responsibility was to share his conflict with his subjects.

Several adverse events occurred, including the deaths of several monkeys and the serious side effects in subjects receiving similar vector injections as Jesse, that were not reported to the NIH and FDA as required. If Dr. Wilson's primary interest was the integrity of his research findings and his patient's welfare, why was there significant non-compliance with the agency procedures? It is important to recognize that reporting such events could have had a negative impact of the future of Dr. Wilson's research. Had the FDA and NIH been aware of so many adverse events and stopped Dr. Wilson's clinical trials, the potential for commercialization of his patents, and the potential for growth of his stock value in Genovo, would have diminished significantly. Did this possibility play into Dr. Wilson's thinking when he did not properly follow federal regulatory guidelines?

Many of these questions will remain unanswered, as there is no clear way to measure the extent to which, if at all, Dr. Wilson's financial interests interfered with his primary interests. By the nature of his position, however, Dr. Wilson's responsibility was to place his research and his patients' safety first, and to place the interests of himself and his company at a distant second. Clearly, it was his ethical and legal responsibility to disclose the extent of his financial stake to Jesse and his family and to follow FDA guidelines. Why he chose not to do so remains unanswered, but it seems as if Dr. Wilson himself

has acknowledged some concern about the relationship between himself, Genovo and the University when he stated: "It's not a bad idea, at this point in the year 2000, to take a fresh look going forward."<sup>108</sup>

## **2. Genovo, Inc. and its Corporate Sponsors**

The ethical and legal responsibilities of the companies sponsoring academic research are often overlooked. The focus is most often on the ethics of the researchers and physicians because they have the most direct effect on patient and public welfare. And though biotechnology companies are in business to earn a profit, in contrast to the motivations of researchers and universities, what they do has a direct effect on peoples' lives, both during clinical testing of their products and when their products make it to market. Because these companies have an enormous impact on public welfare and safety, it is their responsibility also to ensure the research performed with their money is done with integrity.

All of the criticisms of Dr. Wilson relating to the death of Jesse Gelsinger also apply to Genovo and its corporate sponsors. By providing substantial funds for the clinical trials at IHGT, Genovo had the right and responsibility to ensure that appropriate research was being conducted there. When adverse events occurred, Genovo's management team should have urged its researchers to follow legal reporting procedures so that any treatments or therapies that the company did eventually commercialize would be legitimately safe and effective. By permitting, or not forbidding, such misconduct during the research process, Genovo could have allowed a potentially very serious gene therapy application to remain in use on other human subjects, and potentially the public at large. Unfortunately, it took Jesse Gelsinger's death, instead of an ethical business decision, to stop the therapy from being tested on more humans. Genovo, Inc. was named as a defendant in the lawsuit brought by the Gelsinger family for the role the company played in Jesse's death.

From a purely business perspective, the situation surrounding Jesse's death was bad for Genovo's bottom line. Had Genovo and the researchers properly reported adverse events to the FDA, their trials may have been put on hold, reevaluated, and even redesigned, a lengthy process that would delay any commercialization of the therapy. However, by allowing the situation to become out of control and culminate with Jesse's death, the trial was stopped altogether, removing any possibility of the company profiting from the experiments. Mismanaging the situation had a negative impact on Genovo's bottom line, and devalued its five-year investment in the Institute at Penn.

Genovo should have also been concerned with Dr. Wilson's role in the agreement with the University of Pennsylvania. The arrangement was clearly problematic, and Genovo should have reevaluated placing Dr. Wilson, as director of the Institute and also as 30% shareholder in the company he started, in charge of the annual grant of four million dollars.

In terms of the other companies involved, Genovo received the majority of its investment from one of the largest international biotechnology companies, Biogen, Inc. As a parent company with substantial investment in Genovo, Biogen had a responsibility to know about the involvement of its subsidiary. Though the agreement gave Biogen a hands-off approach to its relationship with Genovo, the agreement between Genovo and the IHGT should have raised some concern with Biogen's management. Such a close financial arrangement could, and perhaps did, lead to poor research decisions. Biogen and the other corporate sponsors had a responsibility to their shareholders to invest their money wisely. By turning their heads from what was going on, and permitting a problematic relationship to exist between Genovo, Dr. Wilson and the University of Pennsylvania, Biogen and the others did a disservice to their stockholders. Had the more experienced parent companies, particularly Biogen, taken the responsibility to monitor and manage what Genovo was doing, many adverse events may never have gone unreported and the clinical trials at IHGT may not have ended the way they did, with the death of a patient and a wasted five-year investment.

## **3. The University of Pennsylvania**

The University of Pennsylvania did the right thing by opening discussions with its Conflict of Interest Standing Committee regarding the deal it was about to make with Dr. Wilson and Genovo. It was important for Penn to understand from ethicists, faculty members, and attorneys the potential problems that the situation might bring. It was also appropriate for Penn to take extra precautions to monitor the Genovo arrangement, as well as Dr. Wilson's research, which it did in the form of two committees made up of faculty members and administrators. However, by relaxing some of its conflict of interest rules in order to accommodate the arrangement,<sup>109</sup> Penn compromised its pre-determined idea of what financial arrangements are acceptable for its faculty in a research situation.

In addition to relaxing the restrictions on its researchers, Penn put itself into a conflict of interest by agreeing to the Genovo arrangement. The problems that exist when a researcher stands to gain financially from his work also arise when the researcher's institution holds a financial interest in that work. By retaining a 5% equity share in Genovo, the University of Pennsylvania created its own conflict of interest in that it, too, would benefit financially from a successful outcome of the gene therapy trials.

In addition to the equity share, the university's Institute for Human Gene Therapy also became dependent on Genovo for one quarter of its annual budget. A potential for conflict would exist if the university and Genovo disagreed on a matter, particularly an adverse event that would be bad for the company's business. There is pressure to allow the company to have

the final say in how a particular situation is handled because of the University's reliance on the company for financial support.

For the reasons described above, it was the University's responsibility to ensure that the conflicts of interest for its researchers, particularly Dr. Wilson, were appropriate, managed, and disclosed to the patients. It was also Penn's responsibility to not allow itself to create its own conflict of interest that could prevent it from appropriately handling the first responsibility. And while the University was on the right track by establishing two committees to oversee the arrangement, Penn itself may have been conflicted between its own financial gain and the most appropriate decision regarding the arrangement.

#### **4. Jesse Gelsinger**

Jesse Gelsinger had nothing to gain financially from his participation in the OTCD trial. His decision to enter the experiment was based on information he received from his doctor and the researchers involved in the trial. Knowing it would not bring him any direct benefit, Jesse decided to enter the trial with entirely altruistic motivations. The extent of his responsibility was to listen to what he was told about the experiment from his doctors and the researchers, and then make an informed decision whether to participate in the trial.

Based on the information he received, Jesse decided the trial was something he wanted to be involved in. The lawsuit brought by Jesse's family after his death, however, notes that Jesse's decision to participate was not based on complete information and, in some cases, it was based on misinformation. The lack of informed consent included, as quoted from the Civil Complaint:

- a. Understating the risks of the toxic effects of the injection of the adenovirus particles;
- b. Failing to inform Jesse that monkeys injected with the virus had become ill and/or died;
- c. Failing to inform Jesse that patients who had previously participated in the trial suffered serious adverse effects;
- d. Misrepresentation of the fact that prior participants in the study had achieved certain efficacy with respect to the treatment of OTC;
- e. Failing to adequately disclose the extent to which Dr. Wilson and the University had a conflict of interest;
- f. Failing to adequately disclose the financial interest that Dr. Wilson and the University had in relation to the study.<sup>110</sup>

Jesse's father, Paul Gelsinger, has commented on the extent he believes he and Jesse were provided with inadequate or misinformation. At a hearing of a Senate Subcommittee, Paul Gelsinger commented on his son's death. "I was misled...that's what hurt the most. This was not as it was presented." He continued: "It looked safe. It was presented as being safe. Since it would benefit everybody, I encouraged my son to do this."<sup>111</sup>

Jesse fulfilled his responsibility by reviewing the information provided to him, and making a decision based on the costs and benefits he associated with that information. It was the responsibility of the other stakeholders to provide him with accurate and complete information from which he could make an educated decision.

#### **5. Federal Regulatory Agencies**

During the FDA's investigation of the Institute for Human Gene Therapy at Penn, a number of interesting facts came out regarding Penn's compliance with federal regulation. In their response to the FDA's inquiries, the University of Pennsylvania stated that the IHGT did submit data to the FDA regarding toxicity levels of two participants in the OTCD trial before Jesse's participation. Penn was criticized for not reporting such events, but it turns out that they had submitted the information and it had been overlooked by the FDA. The FDA had comprehensive reports on these patients in its possession for more than six months prior to Jesse's death. The FDA should have analyzed such data before they allowed the trial to proceed into the sixth cohort of patients, which included Jesse Gelsinger.<sup>112</sup>

In this instance, Penn did follow the FDA's requirements by submitting a report, and it went unnoticed by the agency. It was clearly the FDA's responsibility to assess the reports submitted by the University and decide whether the trial should continue. Had the FDA fulfilled its responsibility and looked at the report, perhaps the agency would not have approved the next stage of the trial in which Jesse died.

One thing Penn did not do, however, was to report adverse events like the patient toxicity levels to the RAC (Recombinant DNA Advisory Committee of the NIH), which was responsible for dealing with adverse events during gene therapy trials. The FDA was responsible for approving the clinical trials at Penn's Institute for Human Gene Therapy and making sure that the trial's protocol was followed, but the RAC was supposed to receive and deal with reports of adverse events during gene therapy.

However, it has come out after Jesse's death that there was significant confusion within the medical community as to what needed to be reported and to whom. At the Conference for Human Subject Protection and Conflicts of Interest in August, 2000, many speakers alluded to the miscommunication by the FDA and NIH regarding reporting guidelines. At one time, clinical trial protocols were approved by the RAC, along with adverse event and other reporting procedures. However, the RAC's authority changed a number of years ago and all protocol approval went to the FDA. It was, and still is, however, the

responsibility of the RAC to handle all adverse event reports. Many researchers, unaware that it was still their responsibility to report adverse events to the RAC, began dealing only with the FDA. Thus, a number of adverse events went unreported to the NIH and the RAC, which prevented a great deal of clinical trial oversight over the past few years.<sup>113</sup>

It is crucial for all researchers to know what needs to be reported to the government and how to go about doing so. It is the federal government's obligation to inform researchers of necessary regulations so that they can comply appropriately. The speakers at the Conference in August, 2000, were not trying to make excuses for researchers who did not comply with federal regulatory agencies. However, the nature of those federal regulations must be communicated clearly.

In its response to the FDA after Jesse's death, the IHGT stated that it would have benefited from a "Standard Operating Procedures [from the federal government] to help ensure that all necessary communications and notifications to the FDA were made on a timely basis and that clear and unambiguous acknowledgement of such communications was obtained before proceeding to new stages of the trial."<sup>114</sup> With so much confusion as to what needs to be reported, and to whom, there clearly needs to be some pre-specified framework for the oversight of clinical trials so that all parties know what their responsibilities are. At the very least, federal agencies need to make institutions aware of what constitutes an adverse event, what regulatory body that adverse event should be reported to, and within what time frame the regulatory body needs to know about it. It is the federal government's job to oversee human clinical trials so that subjects are protected during experimentation. If an adverse event occurs and the appropriate federal agency is aware of it, there can be an investigation as to whether it was the result of an unforeseen occurrence, or a poor decision on the part of the researcher. There needs to be better federal oversight of human clinical trials so that patients can be protected from the influence of a researcher's secondary interests.

### **VIII. Industry Position**

The situation surrounding the death of Jesse Gelsinger is only one example of the questionable research practices that have adversely affected patients' well being over the past few years. Whether conflicts of interest played a role in Jesse's death or the other incidents that have taken place is difficult to isolate from other factors. However, there is significant evidence, as was provided earlier in this paper, that conflicts of interest can and do affect research decisions. The challenge is to understand the responsibilities of all the stakeholders in a conflict of interest situation, so that conflicts can be properly managed from all sides.

As described during the case analysis, clinical researchers have a clear ethical, moral, and fiduciary responsibility when dealing with patients. There is clear agreement within the medical and ethical community that a patient's welfare and the validity of research findings must be prioritized over any secondary interests. What is not so clear or simple to define, however, is the responsibility of the companies sponsoring the research. How do the pharmaceutical and biotechnology industries acknowledge and respond to their social and ethical responsibilities?

It is interesting to note that none of the websites of the top five largest pharmaceutical companies including Merck, Aventis, Glaxo Wellcome, Novartis and Pfizer, include a corporate code of conduct. Some of the websites make references to ethical practices or provide a mission statement that mentions public safety; however, there are no published codes of conduct that discuss conflicts of interest for any of the companies. Similarly, the Pharmaceutical Research and Manufacturers of America ("PhRMA"), which represents the country's leading research-based pharmaceutical and biotechnology companies (including all of the companies mentioned above), also does not have a statement of principles or a code of conduct for its members.<sup>115</sup> Neither the large pharmaceutical companies mentioned above, nor PhRMA, make reference to conflicts of interest, or provide guidelines for managing relationships with academia.

There is one pharmaceutical company, however, that has a strong company credo, of which it is extremely proud.<sup>116</sup> Johnson & Johnson has a worldwide company philosophy that has guided its business decisions for fifty years. Its credo talks about just and ethical decisions by management, meeting the needs of their customers first, paying for mistakes the company makes, reserves they have created for adverse times, and an overall sense of responsibility toward all of their stakeholders, not only their shareholders. The portion of the credo devoted to the shareholders, states that only after the company operates according to its principles, will the shareholders realize a fair return. Johnson & Johnson recognizes that it is in business to serve its customers, and when that is achieved, it will be rewarded.<sup>117</sup>

Not only does Johnson & Johnson have a credo that sounds impressive, but its business practices reflect all of the credo's sentiments. At no time was this more evident than during the Tylenol crises faced by Johnson & Johnson during the 1980s, when the company's product was contaminated with cyanide and used as a murder weapon. With the company's reputation on the line, company managers and employees made decisions that were inspired by the philosophy embodied in the Credo. The company's reputation was preserved and the Tylenol business was regained.<sup>118</sup>

Johnson & Johnson is one example of a pharmaceutical company that takes its ethical responsibilities seriously, and is not only concerned with making a profit. It has demonstrated its commitment to quality, and its shareholders have been rewarded for it. Even though Johnson & Johnson recalled 31 million bottles of Tylenol with a retail value of more than \$100 million,<sup>119</sup> the brand has flourished because of the ethical implications of the decision and the company's dedication to the safety of its customers. Perhaps the other pharmaceutical companies that do not follow a company credo need a crisis like the

Tylenol situation to help them recognize the responsibility they have to protect the public. It is important to note, however, the nowhere in its Credo does Johnson & Johnson mention or provide guidelines for the management of conflicts of interest.

The lack of an official position toward conflicts of interest by the pharmaceutical industry is similar to the view held by the organization that represents biotechnology companies: the Biotechnology Industry Organization. While its website does provide members with a Statement of Principles<sup>120</sup> which makes reference to informed consent procedures and federal regulation compliance, there is no reference to conflicts of interest. Moreover, at the Conference on Human Protection and Financial Conflicts of Interest held by the NIH in August, 2000, the representative from the Biotechnology Industry Organization had “no official position” to report on conflicts of interest and said his organization was “working on one.” The representative sent to the conference from the Biotechnology Industry Organization was Dr. Angus Grant, director of gene therapy trials at Eventus Pharmaceuticals. At a conference dedicated solely to conflicts of interest in industry sponsored academic research, the main representative from the industry side had no official position to offer.<sup>121</sup>

It is surprising that so many pharmaceutical and biotechnology companies that receive such intense scrutiny regarding their business practices would have no public information regarding their ethical policies. Most corporations, like Johnson & Johnson, are proud to share their strong commitment to public welfare and ethical business decisions. Why are the pharmaceutical and biotechnology industries less inclined to articulate their business practices, particularly in regards to conflicts of interest that have pervaded their work and led to serious problems?

In 1995, a group of health economists developed a code of conduct for the pharmaceutical industry in an effort to manage and reduce bias that comes from industry-sponsored research. The code of conduct, published in the *Annals of Internal Medicine*,<sup>122</sup> made a number of recommendations for pharmaceutical companies to act more ethically when sponsoring academic research. These recommendations included: researchers, not drug companies, controlling the study’s design and publication; companies not withdrawing funding because interim results do not look favorable; companies paying researchers only for the true cost of the research, not additional incentives; and full disclosure of all findings, including the assumptions and methods.<sup>123</sup> These recommendations have not been taken seriously by industry, in that none of its guidelines are followed.

One source that provides insight into the pharmaceutical industry’s position, or lack thereof, toward conflicts of interest is the publication *Pharmaceutical Executive*, the most widely circulated pharmaceutical industry magazine in the United States. A number of articles in the publication reflect the reticence and indifference of the pharmaceutical industry with regard to the conflicts of interest they create in academia. There is an overall sense from many of the publication’s articles that the pharmaceutical industry is apathetic to public concern that conflicts are problematic for researchers and the public. There is no indication from the publication that pharmaceutical companies do or should have any responsibility to the public in conflict of interest situations.

One article in *Pharmaceutical Executive* entitled “Shared Interests”<sup>124</sup> is indicative of the industry’s attitude toward conflicts of interest. The abstract of the article is as follows:

Industry funding for trials inevitably raises the question of conflict of interest. In the eyes of the public, whether such conflict exists is essentially irrelevant -- once financial relationships are exposed, perceptions of impropriety overrule the actual circumstances surrounding such relationships.<sup>125</sup>

Clearly, executives of pharmaceutical companies are concerned, not with the existence of conflicts of interest, but with the public knowing about them. The article dares to say, “whether conflicts exist is essentially irrelevant.”<sup>126</sup> There is no recognition that conflicts of interest do in fact exist, and have the potential to cause serious harm. The main concern from the industry’s perspective is that people might think conflicts exist and, therefore, may be less likely to participate in clinical trials.

The article goes on to tell the story of one pharmaceutical company, Knoll Pharmaceutical, which touted the positive effects of a thyroid medication after academic investigators concluded that there was no difference between that drug and similar products already available. The company required the investigators to sign a statement agreeing that the company could review journal articles prior to publication, and have the final say regarding what was published. When the actual results of the study did come out seven years later, the company had to pay thirty-seven states a total of \$41.8 million to avoid litigation after allegedly claiming that its drug was more effective than others on the market.<sup>127</sup>

The article concludes by stating that events like the Knoll Pharmaceutical incident “shake the public’s confidence, reinforce the view that pharmaceutical companies act in their own interest first, and contribute to feelings of general ill will toward the industry.”<sup>128</sup> There is no indication that the author thinks what Knoll did was inappropriate, and there is no indication that the magazine is at all concerned with the actual implications of pharmaceutical company actions in conflict situations. The only apparent concern is with the appearance of impropriety that contributes to a negative image for the industry.

How does the pharmaceutical industry propose to deal with the negative appearances that are so often associated with pharmaceutical company behavior? In a *Pharmaceutical Executive* article entitled “Clinical Trials’ Black Eye,” the proposed solution is better public relations.<sup>129</sup> The article first discusses the negative perceptions the public has regarding clinical research trials, including the lack of informed consent in recruiting practices and the use of financial incentives for doctors in

research situations. This is problematic for the companies, in that they constantly need more patients for research trials, and negative perceptions associated with the trials make patients reluctant to participate. Instead of recommending that companies discontinue the use of the questionable practices that give clinical trials their shady reputation in the first place, the article suggests a strong PR campaign.

Specifically, the article recommends the following activities: (1) local news campaigns to generate more calls to clinical trial sites, with interviews from physicians, investigators, and health authorities to provide credibility (2) sponsorship of local health fairs to raise awareness of a condition and the trials being conducted for it, and (3) communication materials such as eye-catching posters, turnkey press releases, and other promotional items to create excitement at a trial site.<sup>130</sup> The main focus is to convince the public that clinical trials are safe, with no recommendations from the author for companies to actually make clinical trials safe for the public.

The article concludes by stating that “only public relations can deliver the credibility pharmaceutical companies need to inspire public confidence.”<sup>131</sup> This is clearly not the best, or only, way to improve public confidence in research, and certainly not in a sincere and truthful way. Public confidence could genuinely be inspired by, first, an acknowledgment of the severity of the problems associated with research today and, second, a commitment on the part of the pharmaceutical industry to do something about it. Public relations may act as a band-aid to cover up the negative image that plagues this industry, but the real, underlying concern will remain unless something is done to address the root of the problem.

The pharmaceutical and biotechnology industries could do a few simple things to prevent conflicts of interest from negatively affecting research and patients. There is no social benefit to be derived from a researcher holding equity in a company whose products they are studying. In fact, there is little or no social justification for many of the rewards offered to physicians. Instead of paying researchers huge sums of money as consultants, why not pool those funds and put them to good use?<sup>132</sup> Clearly, there are many fields or institutions that are in great need of the money. Instead of putting so much money into researchers’ pockets in an attempt to obtain favorable results with the potential to bias research, why not support other valuable research endeavors that could benefit society. Similarly, if industry agreed to give researchers full autonomy in the design and publication of research, instead of reviewing and altering results that may be unfavorable to the company, the level of integrity and objectivity of the research would increase. The public would be able to trust that research findings are complete and honest. Finally, if companies agreed to not withdraw their financial support from a researcher if preliminary research results appear to be unfavorable to the company, researchers would not have to worry about losing their grant support, which could terminate their research endeavor altogether.

These suggestions are not new or hard to understand. They are very simple steps that could cut back on the potential for research bias and patient suffering. Recommendations similar to this were proposed by a group of health economists in the *Annals of Internal Medicine*,<sup>133</sup> as mentioned earlier. However, there is a reason that industry members do not follow such simple recommendations; there is no commitment on the part of either the pharmaceutical or biotechnology industry to protect the public from conflicts of interest. Neither the pharmaceutical or biotechnology industry has an official position toward conflicts of interest. Neither industry acknowledges that they play a role or have a responsibility in managing conflicts of interest. While pharmaceutical and biotechnology companies are in business to earn a profit, they have stakeholders whom their business affects, and thus, have a responsibility to act ethically and protect the public.

While industry has not acknowledged its responsibility regarding conflicts of interest since the wave of scrutiny brought by Jesse’s death, the academic side of the relationship has stepped up to its responsibility and taken action to prevent conflicts from affecting research integrity and patient welfare. The American Society of Gene Therapy, an organization made up of 2,600 gene therapy researchers, physicians, and students, has developed a new and extensive policy regarding conflicts of interest for its members.<sup>134</sup> The policy was adopted by the board of directors of the American Society of Gene Therapy, and immediately e-mailed to all of the Society’s members. The same policy was also published in the *Journal of Molecular Therapy*, the official journal of the Society, and sent to the leadership at the NIH and FDA.<sup>135</sup> The conflict of interest policy of the American Society of Gene Therapy reads:

In gene therapy trials, as in all other clinical trials, the best interest of the patients must be always primary. International, national and institutional guidelines on standards of care must be rigorously followed, approved protocols strictly adhered to, serious adverse events promptly reported to all appropriate regulatory and review bodies. Relevant federally and institutionally established regulations and guidelines in financial conflicts must also be abided by. In addition, all investigators and team members directly responsible for patient selection, the informed consent process and/or clinical management in a trial must not have equity, stock options or comparable arrangements in companies sponsoring the trial. The American Society of Gene Therapy requests its members to abstain from or to discontinue any arrangement that is not consonant with this policy.<sup>136</sup>

This policy, put into effect in April, 2000, was well accepted and supported by members of the Society. The Society’s leadership had not received a single complaint from its members regarding the policy as of the Conflict of Interest Conference in August of the same year.<sup>137</sup>



## IX. Conclusion

The current situation in which academic medicine has become increasingly linked with the pharmaceutical and biotechnology industries has its costs and benefits. While this document has focused primarily on the costs of academic-industry relationships, it is important to remember the benefits they foster as well. Without the funding that industry provides, many academic research institutions would not have the money to carry out their fundamental goals, including education, research, and the provision of clinical care.<sup>138</sup> Lee Goldman, Chairman of the Department of Medicine at the University of California at San Francisco, notes that "companies translate biologic advances into useable products for patients. They do it for a profit motive, but they do it, and it needs to be done."<sup>139</sup> Industry money has helped to develop numerous life-saving drugs, as well as discover innovative, potentially effective treatments for the future.

However, when the lines between academia and industry begin to blur, and the goals of two fundamentally different pursuits become one, the potential for conflicts is significant. At its core, research needs to be objective, unbiased, and controlled. When a researcher stands to gain financially from one particular outcome and would, therefore, prefer that outcome over another, the potential for bias exists whether or not the researcher allows his preference to influence his behavior. The issue is not that researchers may consciously choose one outcome over another based on personal motivations, but that significant financial reward has the potential to subtly, even subconsciously, influence professional decision making. Dr. Angell's question is an important one to ask: Are clinical researchers more immune to self-interest than other people?"<sup>140</sup>

Doctors and researchers who insist they could not be influenced professionally by personal gain need only to look at the evidence that suggests that they can. Stelfox et al., in the *New England Journal of Medicine* study, found that authors whose work supported the safety of calcium-channel antagonists had a higher frequency of financial relationships with the drug's manufacturers than authors whose work did not support the safety of these medications.<sup>141</sup> Another study in the *Journal of General Internal Medicine* found that clinical results that favor a new therapy over a traditional one are more likely if the manufacturer of the new therapy funded the study.<sup>142</sup> Yet another study in the *Journal of the American Medical Association* reported that five percent of industry-sponsored cancer drug studies reached unfavorable conclusions about the company's products, as compared with thirty-eight percent of studies with nonprofit funding that reached an unfavorable conclusion.<sup>143</sup> The evidence supports the proposition that secondary interests can influence scientific objectivity.

In the situation at the University of Pennsylvania in which Jesse Gelsinger died, it is much harder to quantify the effects that financial conflicts of interest had on the clinical trial outcomes. The arrangement between the University of Pennsylvania, Dr. James Wilson, and Genovo, Inc. was so complicated that the University set up two committees to oversee it.<sup>144</sup> Dr. Wilson had a great deal to gain should his use of gene therapy treatments prove to be effective. Did his desire for that reward compromise his judgment as a researcher?

Nobody can claim with absolute certainty that financial interests had anything to do with Jesse's death. However, because Jesse and his family were not made aware of the extent that Dr. Wilson could gain financially from the trial, it leads one to think that such information was not fully disclosed for a reason. If Dr. Wilson was confident in his ability to keep his personal motivations separate from his professional responsibilities, why was this not openly communicated to the Gelsingers before the clinical trial? If the conflicts of interest had been disclosed upfront, anything that went wrong during the trial might have been considered a research-related complication, which the Gelsingers understood as a risk of the trial. What the Gelsingers did not understand as a risk of the trial was the strong self-interest of the researcher. Had the family been aware of the conflicts upfront, the questions of impropriety that surrounded Dr. Wilson after Jesse's death would not have been as strong, and Jesse's family would not have felt deceived or misled.

The lawsuit brought by the Gelsinger family after Jesse's death was settled out of court for an undisclosed sum of money. Dr. Wilson, the University of Pennsylvania, and Genovo, Inc. were ordered to pay damages to the Gelsinger family. Two of the other physicians named as defendants in the suit, the former dean of Penn's Medical School, William Kelley, and the head of Penn's Medical Ethics Program, Arthur Caplan, were dismissed from the case before the settlement.<sup>145</sup> It is also interesting to note that subsequent to the settlement, Genovo Inc. was sold to a biotechnology company called Targeted Genetics, and Dr. Wilson received \$13.5 million in stock as a result of the sale.<sup>146</sup>

When things go wrong, it is easy to place the blame on researchers for accepting financial incentives from industry. They have the most direct impact on patient's safety during clinical trials. However, the role of industry itself must not be overlooked. Why do pharmaceutical and biotechnology companies offer such lucrative deals to academic researchers? The reason is that they want the researcher to think positively about the company. There is no social benefit to be achieved by offering a researcher equity interests or stock options in a company. The intent can only be to build goodwill between the company and the researcher, or worse, to buy the results the company wants. There is clearly no ethical reason for these arrangements to exist. The American Society of Gene Therapy has acknowledged this fact by requesting its members to not accept equity interest, stock options, or comparable arrangements in a company sponsoring the research.<sup>147</sup> The money spent by the pharmaceutical and biotechnology industries to reward researchers for their support would be much better spent on other positive research endeavors. Industry needs to stand up to its responsibility to protect the public from unnecessary harm, and that starts with eliminating unnecessary rewards for researchers. This is not to suggest that industry-academic collaboration should be eliminated. On the contrary, industry support of academia is necessary and beneficial when used appropriately and ethically. It is only when the rewards are exorbitant and unnecessary that problems arise.

Conflicts of interest are a part of medical research today, and this is not going to change. There is simply not enough federal money to support all of the research that needs to be conducted. However, to prevent conflicts of interest from influencing professional judgment, the financial incentives offered to researchers need to be kept under control. The code of conduct proposed by the group of health economists in the *Annals of Internal Medicine* in 1995<sup>148</sup> would help to alleviate many of the problems that can arise. If drug companies only paid researchers for the true cost of the research, there would be less chance for bias in that the researcher would not have anything to gain financially from one particular outcome. However, this would require a strong commitment by the pharmaceutical and biotechnology industries to avoid sponsoring conflicts of interest and start protecting the public from the harm they can cause.

#### Footnotes

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<sup>1</sup> Marcia Angell, *Is Academic Medicine for Sale?* 342(20) NEW ENG. J. MED. 1516 (2000) (discussing gifts from pharmaceutical companies to doctors).

<sup>2</sup> *Id.*

<sup>3</sup> *Id.*

<sup>4</sup> Human Subject Protection and Financial Conflicts of Interest Conference (“Transcript”), at <<http://ohrp.osophs.dhhs.gov/coi/index.htm>> (last visited Feb. 17, 2001).

<sup>5</sup> Angell, *supra* note 1, at 1516.

<sup>6</sup> *Id.*

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

<sup>8</sup> Tinker Ready, *Science for Sale*, THE BOSTON PHOENIX online, at <<http://www.bostonpheonix.com/archive/features/99/04/29/SCIENCE.html>> (last visited Jan. 8, 2001).

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

<sup>10</sup> Sheryl Gay Stolberg, Biomedicine is Receiving New Scrutiny as Scientists Become Entrepreneurs, N.Y. TIMES, Feb. 20, 2000, at 26.

<sup>11</sup> D.F. Thompson, *Understanding Financial Conflicts of Interest*, 329(8) NEW ENG. J. MED. 573, 574 (1993) (discussing how large financial rewards and close relationships with industry are more likely to affect professional decision making).

<sup>12</sup> John McKenzie, *A Conflict of Interest?* Feb. 17, 2000, at

<[http://more.abcnews.go.com/onair/closerlook/wnt\\_000217\\_cl\\_wrongmeds\\_feature.html](http://more.abcnews.go.com/onair/closerlook/wnt_000217_cl_wrongmeds_feature.html)> (last visited Feb. 28 2001).

<sup>13</sup> Angell, *supra* note 1, at 1516.

<sup>14</sup> Eyal Press & Jennifer Washburn, *The Kept University*, THE ATLANTIC ONLINE, at <<http://www.theatlantic.com/issues/2000/03/press.htm>> (last visited Feb. 17, 2001).

<sup>15</sup> Stolberg, *supra* note 10, at 26.

<sup>16</sup> Press & Washburn, *supra* note 14, at Part 3.

<sup>17</sup> Angell, *supra* note 1, at 1516.

<sup>18</sup> University and Small Business Patent Procedures (Bayh-Dole) Act of 1980, Pub. L. No. 96-517.

<sup>19</sup> Michael D. Witt & Lawrence O. Gostin, *Conflict of Interest Dilemmas in Biomedical Research*, 271(7) JAMA, 547, 547-551 (1994) (discussing how the Bayh-Dole Act has affected academic-industry collaboration).

<sup>20</sup> Angell, *supra* note 1, at 1516.

<sup>21</sup> *Id.*

<sup>22</sup> Stolberg, *supra* note 10, at 26.

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

<sup>24</sup> Witt & Gosten, *supra* note 19, at 548.

<sup>25</sup> Angell, *supra* note 1, at 1516.

<sup>26</sup> David A. Shaywitz & Dennis A. Ausiello, A Booming Partnership: University and Industry. Patients Benefit, Too, Though We Should All Be Vigilant, THE BOSTON GLOBE, Sept. 24, 2000, at F3.

<sup>27</sup> Angell, *supra* note 1, at 1516.

<sup>28</sup> Steve Benowitz, *Lines Disintegrating Between Industry, Academic Research*, 92 J. NAT'L. CANCER INST. 1377, 1377-1378 (2000) (discussing the importance of industry funding to new drug development).

<sup>29</sup> Shaywitz & Ausiello, *supra* note 26, at F3.

<sup>30</sup> Witt & Gosten, *supra* note 19, at 547.

<sup>31</sup> Thompson, *supra* note 11, at 573.

<sup>32</sup> Witt & Gosten, *supra* note 19, at 548.

<sup>33</sup> Thompson, *supra* note 11, at 573.

<sup>34</sup> Euthanasia, Microsoft® Encarta® Online Encyclopedia 2000, at <<http://encarta.msn.com>> © 1997-2000 Microsoft Corporation (last visited Jan. 13, 2001).

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- <sup>35</sup> Thompson, *supra* note 11, at 573.
- <sup>36</sup> Henry Thomas Stelfox et al., *Conflicts of Interest in the Debate over Calcium-Channel Antagonists*, 338(2) NEW ENG. J. MED. 101, 101-106 (1998) (discussing the results of a study that indicate that researchers who receive money from a company are more likely to support a drug manufactured by that company).
- <sup>37</sup> *Id.*
- <sup>38</sup> Richard Wolfson, *Pharmaceutical Money Drives the Medical Profession*, at <<http://www.concentric.net/~Rwolfson/PharmaceuticalMoney.html>> (last visited Jan. 8, 2000) (discussing the Stelfox study in the New England Journal of Medicine, and the effects of pharmaceutical money on researcher's behavior).
- <sup>39</sup> Shaywitz & Ausiello, *supra* note 26, at F3.
- <sup>40</sup> See Wolfson, *supra* note 38.
- <sup>41</sup> Press & Washburn, *supra* note 14, at Part 2.
- <sup>42</sup> Shaywitz & Ausiello, *supra* note 26, at F3.
- <sup>43</sup> Richard A. Knox, At NEJM, Clash Over Connections New, Old Editors Differ on Conflict of Interest Regulations, THE BOSTON GLOBE, May 18, 2000, at A1.
- <sup>44</sup> Ready, *supra* note 8.
- <sup>45</sup> Press & Washburn, *supra* note 14, at Part 1.
- <sup>46</sup> Shaywitz & Ausiello, *supra* note 26, at F3.
- <sup>47</sup> Angell, *supra* note 1, at 1517.
- <sup>48</sup> *Id.*
- <sup>49</sup> Wolfson, *supra* note 38.
- <sup>50</sup> University and Small Business Patent Procedures (Bayh-Dole) Act of 1980, Pub. L. No. 96-517.
- <sup>51</sup> Stolberg, *supra* note 10, at 26.
- <sup>52</sup> *Id.*
- <sup>53</sup> Diane Kaminski, Dozens More Adverse Events Reported in *Gene Therapy* Trials, MEDICAL INDUSTRY TODAY, Feb. 4, 2000 (discussing the potential capabilities of gene therapy).
- <sup>54</sup> STOLBERG, *supra* note 10, at 26.
- <sup>55</sup> *Id.*
- <sup>56</sup> Tim Friend, *It's in the Genes: Scientists Confront Issues*, USA TODAY, Feb. 22, 2000 (visited Jan. 8, 2001) <<http://usatoday.com/life/health/genetics/therapy/lhgh024.htm>>.
- <sup>57</sup> *Id.*
- <sup>58</sup> Stolberg, *supra* note 10, at 26.
- <sup>59</sup> Witt & Gosten, *supra* note 19, at 548.
- <sup>60</sup> Trudo Liclur Lemmens & Peter A. Singer, *Bioethics for Clinicians: Conflict of Interest in Research, Education, and Patient Care*, 159(8) CAN. MED. A. J. 960, 964 (1998) (discussing different strategies for managing conflicts of interest).
- <sup>61</sup> Thompson, *supra* note 11, at 576.
- <sup>62</sup> Lemmens & Singer, *supra* note 60, at 965.
- <sup>63</sup> Thompson, *supra* note 11, at 576.
- <sup>64</sup> IRB Homepage, at <<http://www4.nas.edu/irb.nsf>> (last visited Jan. 17, 2001).
- <sup>65</sup> Thompson, *supra* note 11, at 576.
- <sup>66</sup> 42 CFR 50, Sections 50.601 to 50.607 (1995).
- <sup>67</sup> Summary of Federal Law, The Catholic University of America-Office of General Counsel Homepage, at <<http://counsel.cua.edu/FEDLAW/Phs.htm>> (last visited Feb. 11, 2001).
- <sup>68</sup> Mildred K. Cho et al., *Policies on Faculty Conflicts of Interest at US Universities*, 284(17) JAMA. 1590 (2000) (discussing the PHS regulations regarding conflicts of interest).
- <sup>69</sup> *Id.*
- <sup>70</sup> *Id.*
- <sup>71</sup> *Id.*
- <sup>72</sup> Deborah Wilson & Rick Weiss, *Is Jesse's Death a Stain on Science?* THE AGE, Dec. 5, 1999, at <<http://www.theage.com/au/news/19991205/A17092-1999Dec4.html>> (last visited Jan. 6, 2001).
- <sup>73</sup> Joseph DiStefano et al., *Pennsylvania Biotechnology Researcher Negotiates Corporate Funding*, THE PHILADELPHIA INQUIRER, Feb. 27, 2000 (discussing Dr. James Wilson).
- <sup>74</sup> Wilson & Weiss, *supra* note 72.
- <sup>75</sup> Distefano et al., *supra* note 73.
- <sup>76</sup> *Id.*
- <sup>77</sup> Sherman, Silverstein, Kohl, Rose & Podolsky, Complaint—Civil Action, at <<http://www.sskrplaw.com/links/healthcare2.html>> (last visited Jan. 13 2001). A lawsuit was filed in the Philadelphia County Court of Common Pleas, Trial Division by the Gelsinger family against the University of Pennsylvania, James Wilson, M.D., Genovo, Inc., and other physicians at the University of Pennsylvania. Part of this case study is drawn from

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allegations in the complaint filed in the lawsuit. The lawsuit was settled out of court for an undisclosed amount of money.

<sup>78</sup> Wilson & Weiss, *supra* note 72.

<sup>79</sup> Distefano et al., *supra* note 73.

<sup>80</sup> Civil Complaint, *supra* note 77.

<sup>81</sup> *Id.*

<sup>82</sup> Distefano et al., *supra* note 73.

<sup>83</sup> Civil complaint, *supra* note 77.

<sup>84</sup> Genovo Member Profile, (visited Jan. 13, 2001) <<http://www.bio.org.memberprofile/genovo>>.

<sup>85</sup> Distefano et al., *supra* note 73.

<sup>86</sup> Civil Complaint, *supra* note 77.

<sup>87</sup> Distefano et al., *supra* note 73.

<sup>88</sup> Civil Complaint, *supra* note 77.

<sup>89</sup> *Id.*

<sup>90</sup> Distefano et al., *supra* note 73.

<sup>91</sup> Civil Complaint, *supra* note 77.

<sup>92</sup> Distefano et al., *supra* note 73.

<sup>93</sup> *Id.*

<sup>94</sup> Wilson & Weiss, *supra* note 72.

<sup>95</sup> Statement on the Death of Jesse Gelsinger. Institute for Human Gene Therapy Home Page, at <<http://www.med.upenn.edu/ihgt/>> (last visited Dec. 11, 2000).

<sup>96</sup> Wilson & Weiss, *supra* note 72.

<sup>97</sup> Distefano et al., *supra* note 73.

<sup>98</sup> Wilson & Weiss, *supra* note 72.

<sup>99</sup> Civil Complaint, *supra* note 77.

<sup>100</sup> Nadia S. Halim, *Gene Therapy Institute Faces Uphill Battle* 14(3) THE SCIENTIST Feb. 7, 2000, at <[www.the-scientist.com/yr2000/feb/halim\\_pl\\_000207.html](http://www.the-scientist.com/yr2000/feb/halim_pl_000207.html)> (last visited Jan. 21, 2001).

<sup>101</sup> Civil Complaint, *supra* note 77.

<sup>102</sup> Halim, *supra* note 100.

<sup>103</sup> Huntly Collins & Shankar Vedantam, *University of Pennsylvania Plans Review of Gene-Therapy Research*, THE PHILADELPHIA INQUIRER, Jan. 23, 2000 (discussing the FDA's concerns regarding the safety of Penn's IHGT's clinical trials).

<sup>104</sup> Halim, *supra* note 100.

<sup>105</sup> Collins & Vendatam, *supra* note 103.

<sup>106</sup> Halim, *supra* note 100.

<sup>107</sup> Distefano et al., *supra* note 73.

<sup>108</sup> *Id.*

<sup>109</sup> *Id.*

<sup>110</sup> Civil Complaint, *supra* note 77.

<sup>111</sup> Father says Gene Therapy Team Misled Him, USA Today, Feb. 2, 2000 (quoting Paul Gelsinger in regard to Jesse's decision to participate in the trial).

<sup>112</sup> Response to FDA. Institute for Human Gene Therapy Home Page, at <<http://www.med.upenn.edu/ihgt/>> (last visited Dec. 11, 2000).

<sup>113</sup> Transcript, *supra* note 4.

<sup>114</sup> Response, *supra* note 112.

<sup>115</sup> Pharmaceutical Research and Manufacturers of America web site, at <<http://www.phrma.org>> (last visited Feb. 11 2001).

<sup>116</sup> Credo. Johnson & Johnson web site, at <[http://www.jnj.com/who\\_is\\_jnj/cr\\_index.html](http://www.jnj.com/who_is_jnj/cr_index.html)> (last visited March 1, 2001).

<sup>117</sup> *Id.*

<sup>118</sup> *Id.*

<sup>119</sup> *The Tylenol Crisis: How Effective Public Relations Saved Johnson & Johnson*, at <<http://www.personal.psu.edu/users/w/x/wxk116/tylenol/crisis.html>> (last visited July 17, 2001).

<sup>120</sup> Statement of Principles, Biotechnology Industry Organization Home Page, at <<http://www.bio.org/bioethics/principles.html>> (last visited Jan. 13, 2000).

<sup>121</sup> Transcript, *supra* note 4.

<sup>122</sup> *Code of Conduct for Drug Studies Devised by Group*, WALL ST. J. July 3, 1995, at 3A (discussing a proposed code of conduct for industry, published by a group of health economists in The Annals of Internal Medicine).

<sup>123</sup> *Id.*

<sup>124</sup> Carolyn Peterson, *Shared Interests*, PHARMACEUTICAL EXECUTIVE, Aug. 2000, at 154 (discussing the public's perception of conflict of interest problems).

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<sup>125</sup> *Id.*

<sup>126</sup> *Id.*

<sup>127</sup> *Id.* (discussing a situation involving Knoll Pharmaceutical, in which the company was criticized for withholding researcher's true findings and having to pay damages to thirty-seven states seven years later).

<sup>128</sup> *Id.* at 155.

<sup>129</sup> Laura Schoen, *Clinical Trials' Black Eye*, PHARMACEUTICAL EXECUTIVE, Dec. 1999, at 50-56 (proposing solutions to deal with the negative image that surrounds the pharmaceutical industry).

<sup>130</sup> *Id.* at 51-53.

<sup>131</sup> *Id.* at 54.

<sup>132</sup> Angell, *supra* note 1, at 1517.

<sup>133</sup> Code of Conduct, *supra* note 122.

<sup>134</sup> *Membership*, The American Society of Gene Therapy Homepage, at <<http://www.asg.org/membership.html>> (last visited May 11, 2001).

<sup>135</sup> Transcript, *supra* note 4.

<sup>136</sup> *Policy on Financial Conflict of Interest in Clinical Research*, The American Society of Gene Therapy Homepage, at <<http://www.asg.org/policy/index.html>> (last visited May 11, 2001).

<sup>137</sup> Transcript, *supra* note 4.

<sup>138</sup> Angell, *supra* note 1, at 1516.

<sup>139</sup> Thomas Bodenheimer, *Uneasy Alliance -- Clinical Investigators and the Pharmaceutical Industry*, 342(20) NEW ENG. J. MED. 1539, 1539-44 (2000) (quoting Lee Goldman, Chairman of the Department of Medicine at the University of California at San Francisco, regarding the role industry plays in developing products for patients).

<sup>140</sup> Angell, *supra* note 1, at 1517.

<sup>141</sup> Stelfox et al., *supra* note 36, at 101.

<sup>142</sup> R.A. Davidson, *Source of Funding and Outcome of Clinical Trials*, 1 J. GEN. INTERNAL MED.155, 157 (1986), (discussing the affect industry funding has on the outcome of clinical trial results).

<sup>143</sup> M. Friedberg, et al., *Evaluation of Conflict of Interest in Economic Analyses of New Drugs Used in Oncology*, 282 JAMA. 1453, 1453 (1999) (discussing the association between favorable research results and industry sponsored cancer-drug trials — versus non-profit funding).

<sup>144</sup> Distefano et al., *supra* note 73.

<sup>145</sup> Huntly Collins, *Penn, Family Settle Suit in Gene Therapy Death*, at <[http://inq.philly.com/content/inquirer/2000/11/04/front\\_page/GENE04.htm](http://inq.philly.com/content/inquirer/2000/11/04/front_page/GENE04.htm)> (last visited May 6, 2001).

<sup>146</sup> *Id.*

<sup>147</sup> *Policy on Financial Conflicts of Interest in Clinical Research*, *supra* note 136.

<sup>148</sup> Code of Conduct, *supra* note 122.