

COMMERCIALIZATION IN THE U.S. DRUG BUSINESS:**VINCENT DI NORCIA PHD**

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**© VINCENT DI NORCIA PHD 2011***Everything Flows.* Heraclitus**ABSTRACT**

Academic medicine, Marcia Angell claims, is for sale. She and Jerome Kassirer, both former editors of the New England Journal of Medicine, are concerned about the U.S. pharmaceutical industry. The problem is that it treats healthcare and pharmaceuticals as high-priced market goods, which tend to subordinate safety and efficacy concerns to corporate demands for high profits, its payments and gifts involve healthcare professionals in conflicts of interest, its approach to funding clinical trials and medical research has interfered with the integrity of scientific research, it is often not very innovative, and it lobbies against more cost-effective government regulation and improvements of the U.S. healthcare system. Both authors propose a variety of solutions, such as a stronger, more focused FDA regulation of pharmaceuticals safety, efficacy and costs, an end to conflict of interest, full openness in medical research, and more restrictive patents, among others. And there are a few signs of change, albeit not nearly enough.

## COMMERCIALIZATION IN THE U.S. DRUG BUSINESS:

### VINCENT DI NORCIA PHD

Is academic medicine for sale?

Marcia Angell. *The Truth about the Drug Companies.*<sup>1</sup>

The drug industry is not “the Evil Empire. It is an equal partner in the health care endeavor, and we could improve matters substantially by encouraging a more equal partnership.

Jerome Kassirer. *On the Take.*<sup>2</sup>

Marcia Angell first posed her question in an editorial in the *New England Journal of Medicine* (NEJM). In the next issue a reader responded: “No. the current owner is very happy with it.” Nonetheless modern healthcare and drug development would soon shudder to a halt without the support of the pharmaceutical industry. But that same industry is involved in questionable payments, conflicts of interest, and threats to professionalism, as Jerome Kassirer (also a former *NEJM* editor) contends in *On the Take*. Angell’s book reinforces his claims and emphasises issues around clinical research and technological innovation. The problem, both authors suggest, is that drug companies tend to:

- (1) Treat pharmaceuticals as a market commodity,
- (2) Sell healthcare products and services at excessive high prices so as to maximize their equally excessive profits, with the result that...
- (3) Commercial concerns tend to override scientific openness, sound research, weaken their commitment to technical innovation, and at times put patient health at risk.

To explain and support Angell’s and Kassirer’s case we should first follow the money.

### The Money Trail

Pharmaceutical industry profits, Angell claims, ranged from 10 to 25 percent of sales in 2002, more than all the other *Fortune 500* firms combined.<sup>3</sup> The ten top American drug firms averaged profits of 17 percent of sales, almost four times the 4.6 percent *Fortune 500* average. with Pfizer achieving an astonishing 26 percent of sales. Profit rates in related health care equipment and services sectors averaged in contrast only 3.8 percent.<sup>4</sup> Drug company profits seem to go more to marketing and administration (35%), including high executive compensation, than to researching and developing new therapies. Consequently, safe, effective, but cheap, low cost drugs are not developed, and those in need may not get the drugs they need. In 2004 for example Johns Hopkins researchers discovered that an off-the-shelf compound could arrest liver cancer growth in rats. It would cost 70 cents a day, but no drug company showed interest in developing the drug for human use.<sup>5</sup>

“Excess profits are the result of excess prices,” Angell argues, “and prices are excessive principally in the United States, the only advanced country that does not limit pharmaceutical price.”<sup>5</sup> TAP Pharmaceuticals for instance charged Medicare \$500 a dose for its prostate cancer

drug Lupron, TAP sold it directly to doctors for only \$350, leaving them with a \$150 incentive to prescribe Lupron.<sup>1 (p. 130f)</sup> In 1996 however TAP and some of its employees were charged with health care fraud for offering Joseph Gerstein, a Tufts, Massachusetts Health Management Organization (HMO) Director of Pharmacy, a \$65,000 “educational discount” to list Lupron. TAP, Abbott, Astrazeneca, and Bayer pleaded guilty to criminal charges related to health care fraud and paid \$885 million in settlements and fine. In addition some pharmaceutical benefits management companies (PBMs) have been charged with colluding with drug companies to keep prices high and defrauding Medicare and Medicaid.<sup>1 (p. 230)</sup> In Massachusetts eight PBMs were required to pay \$2.2 billion in fines and lawsuit settlements. Since PBMs “negotiate prices and determine what drugs were prescribed”, they threaten the market power of the drug manufacturers.<sup>6</sup>

Brand name prescription drug prices are the fastest growing healthcare cost, rising at 12 percent per year.<sup>7</sup> Pfizer for example raised Claritin’s price 13 times in 5 years for a total increase of 50 percent. Yet an AIDS treatment that sells for over \$10,000 in the U.S., Angell notes, costs as little as \$300 a year in Africa.<sup>1 (p. 206f)</sup> The high prices put many prescription drugs beyond the means of many Americans.<sup>8 9</sup> In fact, *Newsweek* reports, “seven percent of Americans have stopped taking their prescription pills”, because of their high cost.<sup>10</sup> The industry’s devotion to high prices and profits, can only be seen as significant contributing factors to the lamentable lack of affordable and accessible healthcare in the U.S.

Furthermore a 2002 survey reported that 80% of doctors on clinical practice guideline panels had financial ties to drug makers.<sup>11</sup> Drug companies often make undisclosed payments over \$100 to physicians and medical researchers, and at times exceeding \$1000.<sup>12</sup> Pharmaceutical firms offer researchers, experts, and doctors questionable payments and perks, like gifts, and free trips to expensive resorts for conferences on the firm’s drugs. Indeed Dr. C. R. Barksdale of Montgomery, Alabama finds it “hard to believe that it is wrong for a drug company to try to influence the sales of their products by ‘feathering’ the nest of physicians. Isn’t that the American way?” After all, celebrities and politicians “get paid to push some product.”<sup>2 (p. 67)</sup>

That is, unfortunately, the problem. Doctors with close relations to drug companies may see data about the company’s products in a more positive light and prescribe their costlier brand name drugs. A former Eli Lilly sales representative for example told the *New York Times* that drug makers seduce doctors with financial inducements, such as trips to learn about their drugs: “If a doctor says that he got flown to Maui, stayed at the Four Seasons—and it didn’t influence him a bit? Please.” Drug company payments can also lead doctors to prescribe overly high dosages. Oncologists who received \$100 for prescribing 32 milligrams of Zofran for chemotherapy nausea, for instance, did so even though eight would have been equally effective.<sup>2 (p. 36)</sup> 35 percent of the 685 authors who replied to a recent *Nature* survey moreover declared conflicts of interests, based on payments from drug companies for consulting, speaking, doing research, or owning company stock. “The numbers in the survey are distressing.” Drummond Rennie, deputy editor of JAMA, declared, “Drug company sponsors see guideline-issuing bodies as perfect places to exert influence. The practice stinks.”<sup>13</sup>

Minnesota state records show that from 1997 to 2005 companies paid over 5,500 healthcare workers \$57 million.<sup>11</sup> Over 20 percent of state-licensed physicians received on average \$10,000 from drug makers. Ten doctors received more than \$500,000, and around 250

psychiatrists received \$6.7 million—more than any other medical specialty. The services they provided included lectures on drugs and serving on treatment guideline committees. “It beats talking to little old ladies about their bowels”, noted Dr. E. Storvick, who received over \$174,000 from drug companies. Dr Richard Grimm, a blood pressure expert at Minnesota’s Berman Centre for Outcomes and Clinical Research, who has served on hypertension prescription guideline panels, for example earned over \$798,000 from drug companies. In 2003 alone Pfizer paid him more than \$231,000. “It’s the nature of drug companies to make money.” Grimm claims. “They’re not really trying to improve anybody’s health except if it makes them money.” Dr. Donald Hunninghake, a former university researcher who became a full time industry consultant, served on a cholesterol lowering pill guidelines advisory panel in 2004. It recommended that far more people get the drugs; but eight of its nine members had financial ties to drug companies. Hunninghake himself earned \$420,800 from drug makers between 1997 and 2003. In 1998 alone Pfizer paid him \$147,00. The median payment per consultant was \$1,000, and 100 persons received more than \$100,000. “The hope” notes Gene Carbona, a former Merck sales representative, “is that a silent quid pro quo is created. I’ve done so much for you, the only thing I need from you is that you write more of my products.” Because of such dubious inducements, she claims, drug firms “face a tidal wave of investigations and lawsuits.”<sup>1</sup> (p. 130f)

Medical experts who write clinical guidelines are not always impartial. Over 25% of the drug experts the FDA uses as advisers are reported to have a financial conflict of interest.<sup>14</sup> Ten of the 32 FDA advisers who voted in 2005 to allow painkillers Bextra and Vioxx to stay on the market despite safety concerns about cardiac and cancer risks, had taken money from the drug makers.<sup>15 16</sup> The meetings of a nine person FDA panel that recommended aggressive use of enzyme replacement drugs for kidney failure were paid by for one of the two manufacturers. All the panel’s members had financial ties to one of the firms, and the research cited involved merely anecdotal evidence. Many NIH scientists also consult for drug companies, own pharmaceutical stocks, and receive compensation for testing their drugs from pharmaceutical companies. But when the NIH sought to prohibit its 17,500 employees from accepting outside employment or consulting for drug, medical or biotech companies, or owning stock in them, many employees were outraged. Their hostile reaction led the NIH to apply the stock ownership restrictions only to senior staff.<sup>17</sup> Dr. Daniel Carlat was for a year paid by Wyeth pharmaceuticals, \$500 for a one hour “canned talks” to doctors that touted its antidepressant Effexor XR, but quit after a year, as he became more uncomfortable that he found himself “minimizing the hypertension risks”, and withdrawal symptoms it involved, and coming to the realization he was being paid to enthusiastically endorse the drug” rather than offer a balanced scientific, truly educational presentation.<sup>18</sup> The American Heart Association (AHA) for instance published a guideline recommending Altephase, a stroke treatment manufactured by Genentech, from whom it had received \$11 million; but it omitted to mention a critical minority report and even deleted the author’s name from the list of researchers. 95 of the 170 experts who worked on the fourth 1994 edition of the *Diagnostic and Statistical Manual of Mental Disorders* for the American Psychiatric Association had financial ties with, or received money from, a drug maker in the previous five years.<sup>19</sup>

Such problems led Donald Kennedy, the editor of *Science Magazine* to protest that the FDA “played softball with the pharmaceutical industry [and] slowed the progress of medical innovation.”<sup>20</sup> It is underfunded, understaffed and overly friendly to the industry it regulates. For investigators who have financial research relationships with pharmaceutical industry are more

likely to favour the company's products over competing products and less likely to criticize their safety or efficacy of their products.<sup>21</sup> In fact their payments to healthcare professionals are in fact so problematic that the U.S. Office of Inspector General (OIG) has been investigating whether they constitute 'fraud and abuse' or illegal kickbacks.<sup>2 (p 149)</sup>

PhRMA (the U.S. pharmaceutical manufacturers trade association), claimed that the payments were not illegal and serve patients' interests because they are used "to make sure medicines are used properly;" but patients usually are not informed about such payments.<sup>22</sup> From 1991 to 2002 PhRMA spent \$558 million on political contributions, related advertising, and the largest political lobby in Washington with 675 lobbyists, more than the members of both houses of the Congress.<sup>1 (p. 198)</sup> The drug companies themselves spent around \$416 million on lobbying for the 2003 prescription drug bill, including contributions to 'stealth' Political Action Committees such as Seniors Coalition and the 60 Plus Association.<sup>23 24</sup> Dr Ron Paul, a Texas Republican called the bill 'Republican Socialism', for enriching pharmaceutical companies at taxpayers' expense and forces millions of Americans to accept inferior drug coverage, while doing little to address the real reasons prescription drugs cost so much.<sup>25</sup> It also made the seniors' drug benefit more complicated to use and banned the import of lower priced drugs from Canada.

In contrast to the U.S. free market approach, Canada's federal and provincial governments each regulate prescription drug prices. The federal Patent Medical Prices Review Board (PMPRB) checks brand name drug prices against the median price in seven developed nations, resulting in prices one half to two thirds of U.S. prices.<sup>26</sup> The PMPRB resisted approving Erbitux, a brand name colorectal cancer drug produced by Bristol Myers Squibb (BMS), which insisted on its high U.S. prices, even though BMS sells it for less than half that price in Europe. BMS even threatened to refuse to market the drug in Canada at a lower price. In response the PMPRB is considering refusing BMS a licence and having the drug made by a generic firm. Provincial healthcare authorities not only negotiate lower prices and volume discounts for their health care insurance programs, their lists also prefer equivalent generics over brand name drugs.<sup>27 28</sup> As a result drug prices are declining in some provinces. It would seem, Angell notes, that governments are more efficient than markets: "The overhead of Medicare [for seniors' healthcare] is one percent. The overhead of the private insurance industry is roughly 20 percent. That's profits and administrative costs... So Medicare is extremely efficient, even [though] they use private carriers."<sup>29</sup>

Interest conflicts can put patient health at risk. Three Seattle doctors, Kassirer reports, were running clinical trials of man-made antibodies to prevent complications from a risky leukemia bone marrow transplant.<sup>2 (p. 160f)</sup> Five patients died during those trials. One had 100,000 shares in Genetic systems, which owned the antibody sequence, another 250,000, and a third 10,000. Two were paid yearly stipends over \$10,000, and one had a three year consulting contract with Genetic Systems.

High drug prices and company profits, claims Angell, have contributed to appallingly high U.S. healthcare costs and the lack of health insurance coverage for 15 percent of the population. It is, Angell comments, as if "we had set out to design the worst system that we could have imagined," for "our life expectancy is shorter. Our infant mortality is higher. ... Canadians see their doctors far more often than we do. Americans can't really afford to see their doctor. There's

always some co-payment, or something isn't covered."<sup>27</sup> In fact U.S. per capita healthcare costs approximate \$4,500 in contrast to around \$2,000 in Canada and \$1,000 in Britain, both of which enjoy universal health insurance.

### Marketing Disease

While health is not a market commodity, drug companies, spend \$25 billion on marketing.<sup>30</sup> Their promotions, Angell claims, "promote diseases to fit their drugs", instead of promoting drugs to treat diseases.<sup>1 (p. 86)</sup> Such "disease-mongering" leads people to purchase drugs they don't need.<sup>31 32</sup> Drug companies for instance spend millions on 88,000 sales representatives to visit doctor's offices and promote their products, leading many physicians to prescribe high-priced brand name drugs over cheaper generics, older drugs, or life style changes in exercise and diet.<sup>1 (p 126f, 170)</sup> Yet brand name drugs at times are less effective than equivalent generics, whose approval the pharmaceutical companies often oppose.<sup>33 1 (p 96f)</sup>

In addition U.S. drug companies use direct-to-consumer (DTC) advertising, being ads they are designed to stimulate consumer demand for the company's products.<sup>34 35</sup> Eli Lilly hired an advertising firm to promote Xigris, a high price (\$6800 a dose) anti-infection treatment. Pfizer for example promotes Lipitor, the highest selling drug in the world (over \$12.9 billion), through its *Lipids Online* website and *Lipids Letter*, which selectively present favourable information about Lipitor. While PhRMA claims such ads help educate patients, they also lead people to self-prescribe, without consulting their physician or pharmacist, who can offer them impartial, balanced advice on all treatment options, such as lifestyle changes and other treatments.<sup>21</sup> That is in part why they are prohibited in other OECD nations, but in the U.S. FDA approval is not required.

DTC ads promote dubious 'off-label' uses for drugs not approved by the FDA.<sup>1 (p. 88f)</sup> Parke – Davis (now owned by Pfizer), for example engaged in an illegal communications strategy for Neurontin, its Prozac-like 'me-too' drug. The publicity, Angell writes, was not only designed to "sell Neurontin on pain." It also promoted a variety of dubious off-label uses: for hot flashes, migraines, tension headaches, insomnia, and also for vaguely defined conditions such as social anxiety disorder, restless legs syndrome, hiccups, nicotine withdrawal, migraine, generalized anxiety disorder, and, Angell adds, "just about anything else you care to name."<sup>1 (p. 205)</sup> In 2004 however Pfizer pleaded guilty to illegal marketing charges and paid a \$430 million fine, which was still only one-sixth of \$2.7 billion, its 2003 Neurontin sales revenue.<sup>1 (p. 161)</sup> For, she cogently notes, it is the overly commercial market approach to health which "has made the health care system so dreadful, so bad at what it does. Yes, it does do what markets are supposed to do. [But health care] should be distributed according to need. If you're very sick, you should have a lot of it. ... Suppose you're poor and ... you have a brain tumor. You're gonna shop for a bargain? ... No. And you can't say 'I'll wait until next year,' either. This is a life and death thing and we ought to treat it that way."<sup>28</sup> In a sense, then, the problems of the pharmaceutical industry are a symptom of the deeper American addiction to free market approaches to non-market, public goods like healthcare, and medical professionalism.

## The threat to Medical Professionalism

The prime moral obligation of healthcare professionals dates from Hippocrates, namely: First, do no harm. Physicians, as the Canadian Medical Association Ethics Code states, must “consider the wellbeing of the patient” ...and “resist any influences that might undermine professional integrity, [and] resist and disclose conflicts of interests,” such as payments or benefits from pharmaceutical companies.<sup>36</sup> The guidelines of the Ontario College of Physicians and Surgeons stipulate that physicians should not invest in drug companies, be inappropriately affiliated with them, or accept fees, gifts or other considerations from pharmaceutical firms.<sup>37</sup> Law, engineering, accounting, and journalism, Kassirer notes, monitor their members’ practices and regulate their obligations to avoid conflicts of interest, serve their clients and the public good, more strictly than does the medical profession. “Why”, he asks, “should the guidelines for reporters be far more stringent than those for doctors?”<sup>2 (p. 200)</sup> In sum patients, notes Cardinal Joseph Bernardin, “have the right to disinterested professional judgement. ...it shouldn’t have to be the patient’s responsibility to protect themselves.”<sup>2 (p. 189f)</sup>

Kassirer has a point. Drug companies not only sponsored the American Thoracic Society’s 2002 lung treatment brochure, it quoted only those remarks of its conference speakers that supported the firm’s products—without their consent. The AMA endorsed Sunbeam household products in exchange for royalties on their sales.<sup>2 (p. 127)</sup> A 2004 report of the American College of Neuropsychopharmacology contended that the benefits of Specific Serotonin Receptor Inhibitors (SSRIs) outweighed any risk of increasing suicidal tendencies in youth, but nine of the ten author/panelists had extensive ties to the pharmaceutical industry.<sup>2 (p. 126)</sup>

A 2004 report of the American College of Neuropsychopharmacology claimed that anti-depressants like SSRIs did not increase suicide risk in youth, so the benefits outweighed the risk.<sup>2 (p. 126)</sup> But Dr. David Healy, a Welch psychiatrist criticized the misuse of SSRIs like Zoloft and Prozac for vaguely defined mood disorders.<sup>38 28</sup> His research showed that, while effective for certain conditions, they often led to serious withdrawal symptoms like anxiety, nightmares, nausea, and suicidal tendencies rather than enhancing peace of mind as claimed. Healy cited the disclosure by Eli Lilly, manufacturer, in its patent application for Paxil, a drug similar to Prozac, that it would be less likely to induce a variety of problems, such as headaches, anxiety, insomnia, suicidal feelings and self-mutilation. Their claims were supported by an FDA warning about SSRI risks—which also noted that placebos were almost as effective.<sup>39</sup> Healy’s critique contributed to the abrupt denial of an offer of a professorship by the University of Toronto.

Excessive commercialism, Angell contends, affects healthcare services too. A HMO’s drive to control costs may conflict with their doctors view that more drugs or treatments are needed than HMO management allows.<sup>33</sup> Not only may money be deducted from their salaries, some are offered bonuses for saving costs by staying within HMO guidelines. HMOs also change physicians prescriptions, second guess their decisions, and restrict their communication with patients. Take the case of Ms. C. Herdrich, cited by Kassirer.<sup>2 (p. 145-6)</sup> Concerned about abdominal pains Ms. Herdrich went to CarleCare, a physician-owned HMO. Dr. L. Pegram, her physician, found an inflamed mass in her abdomen and scheduled an ultrasound to check it out eight days later, at another CarleCare facility 50 miles away. By then Ms. Herdrich’s appendix had ruptured and she needed surgery. She later sued CarleCare and Dr. Pegram for malpractice. The case went to the Supreme Court, who found that Dr. Pegram’s decision to “wait before

getting an ultrasound for Herdrich, ...at a distant facility owned by Carle, reflected an interest in limiting the HMO's expenses, which blinded her to the need for immediate diagnosis and treatment."

### Threats to Scientific Integrity

Good research is essential to developing safe, efficacious treatments, and drug companies support a lot of it, sometimes on a *pro bono* basis. AstraZeneca for example supports a three year \$100 million research project to apply basic discoveries to clinical practice in China.<sup>40</sup> And drug companies are involved in 63 public-private partnership projects targeting diseases that afflict the poor.<sup>41</sup> On the other hand, although clinical trials in Italy showed that melatonin, a cheap food supplement, slows the growth of various cancers in conjunction with conventional treatments, the pharmaceutical industry was not interested in developing the low cost treatment commercially.<sup>42</sup> Instead, drug firms tend to fund research into modifying existing drugs with predictable commercial potential.

The drug industry sponsors about most clinical trials in the US, but in the last few years however industry funding for clinical trials of new drugs directed by academics dropped from 80 percent to 40 percent of funding.<sup>43</sup> The major source of new drugs, Angell claims, is publicly funded research, usually performed by academics.<sup>1 (p. 65, 98)</sup> In addition little is known about contractual provisions which might interfere with researchers academic freedom to control the project and publish their findings. Since, Angell notes, does the FDA require drug firms to disclose the full results of such trials, "we need to question how reliable publications from industry-sponsored research really are", for they often amount to "bogus education about bogus research"<sup>1 (p. 157, 112)</sup> Many Phase IV post-marketing clinical trials of new drugs, Angell feels, are "merely gimmicks to increase sales."<sup>1 (p. 163)</sup> Research articles published with drug company funding tend to favour the company's drugs more than articles not funded by the industry.<sup>44</sup> Indeed many clinical trials are conducted by 'Contract Research Organizations' hired by a drug company.<sup>1 (p. 100f)</sup>

Industry funding may mean all the data from clinical trial and medical research are not published, especially results which don't favour their product.<sup>45 20</sup> When Dr. David Kern, the founder and director of Occupational Medicine At Brown university, published research finding a high incidence of lung disease in workers at a plant with financial ties to Brown university, he was threatened with legal action by the company and dismissed from his academic post.<sup>46</sup> When Dr. Ignacio Chapela's research, published in *Nature*, showed that native corn in Mexico had been contaminated by material from genetically modified corn, was refused tenure in 2003 by the University of California (Berkeley).<sup>47</sup> Chapela had been a vocal critic of a 1998 agreement between the University and Novartis, which offered Berkeley \$5-million each year for five years in exchange for early review of all proposed publications and presentations by faculty members whose work the Novartis funds supported. In 2005 however the new Chancellor, Dr. Robert Birgenau, reviewed Dr . Chapela's case and reinstated him.<sup>48</sup>

In addition, Kassirer writes, there is evidence of bias in industry-supported research, in favour of company products over competing equivalent treatments, even when the latter are cheaper, more effective or safer.<sup>2 (p. 167b)</sup> In 2004 for instance AMGen, which makes the most expensive drugs for treating kidney disease, underwrote more than \$1.9 million for research on

healthcare services for kidney patient and education for the national Kidney Foundation. But Dr. Daniel Coyne, a kidney specialist, views the Kidney foundation's "pro -industry anemia guidelines..." "with great skepticism." He is concerned that Amgen's anemia drugs may have led to more deaths than would normally be expected.<sup>49</sup>

Authorship is another concern. A recent study for the International Council of Medical Journal Editors (ICMJE) found that 74% of publications had ghost authors.<sup>50</sup> Novartis for example owns Intramed, a 'Medical Education' firm, which prepares ghost-written 'research articles' designed to sell its products. Parke-Davis hired Medical Education And Communication Companies to find academic experts who would agree to be listed as authors of such articles, usually for a fee up to \$12,000 for each article, and \$1,000 for the ghost writer. Thus, as one memo said about an author search, "The COMPANY HAS DRAFT COMPLETE. WE JUST NEED AN AUTHOR." (1, p. 159; their caps) It is no wonder, David Korn and Susan Ehringhaus claim, that there is widespread "public skepticism about the timeliness, accuracy, and completeness of reporting clinical trial results."<sup>51</sup>

Some drug company research support contracts require researchers to sign away their autonomy as scientists to monitor and control and analyze data, publish full results, notify institutional review board committees of risks to research subjects, and even communicate health risks to patients. In consequence patient health as well as scientific integrity is put at risk. Roger Darke for example died during the clinical trial of experimental gene therapy, at St. Elizabeth's Medical Centre in Massachusetts, but he had not been informed of the known critical risks of the treatment.<sup>2 (p. 159f)</sup> The principal investigator in the Darke case, Dr. J. Isner, owned 20 percent of Vascular Genetics. Not only had Dr. Isner delayed reporting the death to the research oversight board, he continued to enrol patients in the study after Mr. Darke's death. Or take the well-known case of Dr. Nancy Olivieri, a professor in the University of Toronto medical school.<sup>52 2 (p. 59f)</sup> As part of her research on a prescription drug for thalassemia at the Toronto Hospital for Sick children, Olivieri signed a contract for partial support with Apotex, Canada's largest drug firm. When she found that the new pill was not working well and unacceptably increased patient risk, she published her findings in NEJM, and informed her patients of the risks. As a result, Apotex not only withdrew its support it also sued her for violating its contract. Dr. Olivieri was not supported by her hospital or University, (which last was discussing a multi-million dollar contribution from Apotex at the time), and suffered personal vilification.<sup>53</sup> Fortunately, she has now been fully vindicated.

A recent study of views on commercial funding of clinical trials to which 91 U.S. medical schools responded, found that standards protecting the academic freedom of researchers varied widely, as the following results indicate.<sup>54</sup>

- 24% of the schools surveyed would allow sponsors to insert their own statistical analyses into manuscripts, 47% would not, and 29% were unsure.
- 50% would allow sponsors to draft the manuscript, 40% would not, and 11% were unsure.
- 41% would allow sponsors to prohibit researchers from sharing data with third parties after the clinical trial was over, 34% would not, and 24% were unsure; and

- Disputes about such funding agreements were common: mostly on payments (75%), intellectual property (30%) and access to data (17%).

These results reflect the fact that commerce penetrated academe decades ago. In 1974, Kassirer reports, Harvard Medical School signed a 12 year contract with Monsanto, who would contribute \$23 million to support for biological research.<sup>2 (p. 179)</sup> In return for its support Monsanto was granted an exclusive licence for all new technologies proceeding from the research it funded. The 1980 Bayh-Dole Act encouraged university / business R& D partnerships. Today two thirds of academic medical centres have equity in business start up ventures. In 2001 drug companies paid over 60 percent of medical education. The industry hosted 300,000 so-called, topical 'educational' events in 2001 and 2002.<sup>1 (p. 142)</sup>

In 2005 six major universities reaped an average of \$95 million from Strategic Research Alliances with drug companies (SRAs).<sup>55</sup> Many SRAs are poorly designed, Andrew Webster writes, with the result that "the need to keep corporate sponsors happy is paramount [and] academic researchers are under overt pressure to deliver the goods which the contract with the companies expressly specify." However in well-designed "two track SRAs" research funding would in contrast be at arms length and academic freedom would be respected. There is also a demonstrated need for a commitment to research ethics, and perhaps a clear research ethics code, to facilitate compliance by academe, research institutions, and funding organizations.<sup>56</sup>

### **Imitation rather than Innovation**

Technological innovation is a complex process, distinct from both scientific research and commercial development.<sup>57</sup> Radical innovation is rare, unpredictable and often costly. Firms like HP, IBM, Bell labs and drug companies try to encourage innovative in house R & D.<sup>58</sup> However of the 415 drugs approved by the FDA from 1998 to 2002, only 14 percent were genuinely new (itself a respectable track record), while nine percent were old 'improved' drugs. The remaining 77 percent were me-too drugs.<sup>1 (pp. 74f)</sup> Nor are drug firms as innovative as they claim. PhRMA contends that \$31 billion (14%) of the \$217 billion in 2002 revenues for the top ten pharmaceutical firms, was spent on pharmaceutical new drug development, high compared to other industry sectors;<sup>59</sup> but the industry spends many more millions on marketing, sales, administration, high executive compensation, and an army of Washington lobbyists that outnumbers its legislators.<sup>27</sup> The latter includes lobbying against government regulation of pharmaceuticals, such as an Indian law allowing royalties to generic drug makers.<sup>60</sup>

The pharmaceutical industry seems to have an impressive patent track record, but neither U.S. patent law nor the FDA clearly distinguish between minor modifications, imitations and genuine innovations.<sup>61</sup> The FDA for example approves new drugs which are shown to be better than placebos, rather than requiring rigorous efficacy and safety tests of me-too copycat drugs against older, existing drugs at equivalent dosages. And patent acquisition is a common 'innovation' tactic. In the 1920s for example Hoffman-LaRoche (HLR), a Swiss textiles dye manufacturer, moved into the newly emerging vitamins market and acquired the patents for newly discovered vitamins for a pittance.<sup>62</sup> HLR now controls nearly half the lucrative world market for vitamins. So HLR applied the same tactic to sulfa drugs and tranquilizers. Drug firms are still follow HLR's example.

In fact eight of the top 10 organizations obtaining patents or receiving income from licensing innovations are universities, two are hospitals, and only one is a pharmaceutical firm.<sup>63</sup> Sixteen of the seventeen top patent applications for all new drugs and medical devices in 1998, Angell notes, came from universities; only one was from industry. 54 percent of the research cited in patent applications came from universities, 13 percent from governments and only 15 percent from industry.<sup>1 (p. 64f)</sup> University of Alberta researchers for instance found that an industrial chemical (dichloroacetate) would shrink tumours in animals by up to 75%; but they could not attract commercial support for further clinical testing. So they sought public support instead.<sup>64</sup>

Tinkering with existing drugs and copying them costs firms much less than developing truly new drugs. Clarinex for instance is a Claritin copycat drug, and Paxil, a Prozac copycat drug. Much 'new' drug development only involves minor modifications of existing drugs, to both avoid intellectual property concerns and develop new products that promise high sales and profits. Such considerations underlie Angell's claim that developing a 'new' commercial drug typically costs around \$175 million after taxes, rather than the \$800 million claimed by PhRMA.<sup>1 (p. 38f)</sup>

### **A Need for Change**

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In fine, Angell and Kassirer have shown that the U.S. pharmaceutical industry...

- Reaps excessive profits and overcharges for its products,
- Involves healthcare professionals in conflicts of interest through its payments and gifts,
- Spends far more money on sales and marketing than on innovation,
- Markets disease,
- Is more imitative than innovative,
- Contributes to violating the integrity of scientific research, and
- And contributes to weakening the FDA.

It is therefore evident that, as Angell writes, "the system for the testing, approval, marketing, safety assurance a, and clinical use of prescription drugs is in serious trouble. [They] are far too important to the nation's health for us to ignore the need for thoroughgoing reform."<sup>1 (p. 276)</sup> In fact there are a few small signs of change. New FDA rules would limit advisory panel member's roles.<sup>65</sup> Members who receive money from a drug company or medical device maker would be barred from voting on approving that company's products. Doctors who receive over \$50,000 from that company or a competitor would not be allowed to serve on that FDA advisory panel. The ICMJE has called for truth in authorship, the public registration of clinical trials, and the full publication of research results.<sup>43</sup> *PLoS Medicine* and the American Medical Informatics Association are developing a Global Trial Bank, with which some pharmaceutical trade groups are offering to share data.<sup>66</sup> The American Societies of General Internal Medicine, Psychiatry, Clinical Oncology, and Gene Therapy each resist commercial ties. When the U.S. Academy of Pediatricians accepted money from Ross Products, an infant formula manufacturer, to place its logo on the Academy's 2002 *Guide to Breast Feeding*, members objected, leading the Academy

to refuse such payments and not allow commercial firm or product names on its educational materials. The American Heart Association (AHA) requires its journal editors to eschew conflicts of interests. Harvard Medical School does not allow researchers to test products that they develop on their own patients. The American Medical Student Association forbids residents, students, and physicians from accepting gifts from drug firms.

Much more needs to be done; for “The only way to both reduce cost and increase access and quality is to change the system, scrap it and start over;” for, Angell argues, “we we’re really not getting our money’s worth. ...In Canada where everybody is covered for everything they go to the doctor much more often. When they are hospitalized, their hospital stays are longer.”<sup>27</sup> She and Kassirer therefore argue, in opposition to the pharmaceuticals lobby, for greater government regulation to expand healthcare coverage and reduce healthcare prescription drug costs, bringing the U.S. in line with practices in Canada, France and other developed nations. They also make the following suggestions for change:

- All payments and gifts by healthcare firms to healthcare professionals, medical researchers, journals, and clinical trial subjects should be disclosed. Any which involve a potential conflict of interest should be reported to the relevant professional college for appropriate action.
- The academic freedoms and publication rights of healthcare researchers and academic journals should be legally protected against interference or suppression by business, government, university administrators, or other groups. Universities and hospitals should be prohibited from agreeing to donation conditions that violate academic freedom. Drug company sales / marketing staff should not have any power to determine medical school curricula or the conduct of research into their products. University and hospital / business R&D partnerships should follow the two-track SRA model. Research partnerships should support research on treatments for widespread serious diseases and reducing deaths from adverse drug reactions.
- Angell argues that the FDA should be replaced by a fully independent Institution For Prescription Drug Trials (IPDT), as part of the NIH.<sup>1 (p. 245f)</sup> The IPDT should also ensure that prescription drug research is properly conducted, that clinical trials are rigorously designed so as to determine whether a new drug is safer or more effective than existing drugs, placebos or lifestyle changes for treating the same condition at equivalent doses. All clinical trials should be publicly registered and their results fully reported prior to FDA approval of a drug.<sup>67</sup>
- The FDA should regulate drug prices and reduce them to lower international levels. It should develop a formulary of approved drugs and their uses, and prohibit DTC ads for prescription drugs.
- In addition, I suggest, the IPDT, FDA and the U.S. patent office should work together to ensure that drug patents reward basic science and genuine technical innovation, rather than be granted for copycat drugs or minor modifications of existing drugs. The clock on patents should not begin ticking until a drug is approved by the IPDT and last from six to ten years.

To the extent that the pharmaceutical industry supports such reforms it will contribute to solving the problems of the U.S. healthcare system, rather than being a major part of the problem.

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