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## BOOK REVIEWS

### **The High Cost of Prescription Drugs: The Price of Success?**

**H. Jeffrey Lawrence, M.D.\***

*The Big Fix: How the Pharmaceutical Industry Rips Off American Consumers.*  
By Katharine Greider. *New York: PublicAffairs*, 2003. Pp. 189.

*Magic Cancer Bullet: How a Tiny Orange Pill Is Rewriting Medical History.*  
By Daniel Vasella with Robert Slater. *New York: HarperBusiness*, 2003. Pp. 258.

Two recent books provide radically different perspectives on the pharmaceutical industry. *The Big Fix* by Katharine Greider<sup>1</sup> is squarely in the muckraking tradition of Jessica Mitford,<sup>2</sup> while the *Magic Cancer Bullet* by Daniel Vasella<sup>3</sup> with Robert Slater is a business insider's view on modern drug development. *The Big Fix's* subtitle—"How the Pharmaceutical Industry Rips Off American Consumers"—captures its theme. By contrast, Dr. Vasella develops the notion that modern drug development is

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1. KATHARINE GREIDER, *THE BIG FIX: HOW THE PHARMACEUTICAL INDUSTRY RIPS OFF AMERICAN CONSUMERS* (2003).

2. For one example of Jessica Mitford's investigative work on the American funeral industry, see JESSICA MITFORD, *THE AMERICAN WAY OF DEATH* (1963).

3. DANIEL VASELLA WITH ROBERT SLATER, *MAGIC CANCER BULLET: HOW A TINY ORANGE PILL IS REWRITING MEDICAL HISTORY* (2003).

incredibly complex and expensive, and drug companies take big risks that need to be rewarded with big profits. While opposite in viewpoint, the books share key characteristics. Both are short tomes targeting the lay public. Both put a sharp focus on the issues of fair marketing and pricing practices for prescription drugs. And, by ignoring the potential of physicians to serve as agents of change, both fail to provide concrete steps to alleviate the problem of prescription drug costs in America.

Much of what is covered in Greider's *The Big Fix*, in eight chapters with titles such as "Drugs R Us" and "Patent Shenanigans," is old territory—the rapid rise in expenditures on prescription drugs in the United States, the high profits of pharmaceutical firms, questionable patent manipulations, aggressive marketing practices to physicians and the general public, and the arcane pricing structure of pharmaceuticals. Many of the issues discussed are important and compelling. There is little question that the cost of medication is putting a heavy economic burden on elderly and poor Americans, by some estimates consuming fourteen percent of the average Social Security benefit.<sup>4</sup> The common practice of developing "me-too" drugs—with high price tags but only modest improvements in convenience and/or toxicity—are described.<sup>5</sup> Greider discusses the byzantine pricing practices of American pharmaceutical companies, with consumer costs that drive the elderly to take bus trips to Canada for cheaper medicines.<sup>6</sup>

Perhaps the most critical ethical issue concerning the pharmaceutical company relates to their marketing practices. Greider cites estimates that the drug industry devotes one-quarter to one-third of its sales dollars to marketing,<sup>7</sup> amounts that may exceed the costs of research and development. Like other consumer advocates, she finds these expenditures excessive and largely responsible for the high cost of prescription drugs. However, the pharmaceutical industry has persistently disputed these estimates,<sup>8</sup> and it is difficult, if not impossible, to find firm figures to support either position. That being said, it is hard to believe that

4. Frank Davidoff, *The Heartbreak of Drug Pricing*, 134 ANNALS INTERNAL MED. 1068 (2001).

5. GREIDER, *supra* note 1, at 47-48.

6. *Id.* at 22-23.

7. *Id.* at 64.

8. See, e.g., Melody Petersen, *Increased Spending on Drugs Is Linked to More Advertising*, N.Y. TIMES, Nov. 21, 2001, at C1 (noting that "[t]he big drug companies . . . objected" to a study suggesting a link between advertising and the high cost of prescription drugs and "said that their research showed no direct link between advertising and rising drug expenses").

marketing costs cannot be reduced substantially, given that U.S. consumers paid in excess of \$145 billion in 2000 on prescription drugs.<sup>9</sup>

So why does the pharmaceutical industry devote such large sums of money to advertising? Drug companies are not foolish, and they would not spend billions of dollars on marketing if the medications sold themselves. The medical literature bears out Greider's contention that meetings with drug representatives and the provision of free samples do influence the prescribing practices of physicians and the likelihood that they will request that a new drug be added to their hospital formulary.<sup>10</sup> She also points out that even young idealistic doctors in training are susceptible to the pharmaceutical industry's direct marketing practices, which include giving physicians gifts of expensive meals, books, medical equipment, and even luggage and resort vacations.<sup>11</sup> The Pharmaceutical Research and Manufacturers of America (PhRMA) recently adopted a new Code on Interactions with Healthcare Professionals, which significantly limits gift-giving and entertainment to physicians, but the code is purely voluntary.<sup>12</sup> Hospitals, HMOs, and many medical professional organizations have also adopted stricter codes of ethics that impose limits on the interactions between health care workers and pharmaceutical representatives.<sup>13</sup> But much more could be done. These new codes do not address the issue of direct advertising to consumers on television, radio and magazines. Patients do go to their doctors and ask for the "purple pill" even if they do not know what medical conditions it treats. If large medical organizations and HMOs lobbied government and industry to end direct advertising to the public, direct marketing could be severely curtailed.

What should drive the proper selection of prescription medicines if

9. Davidoff, *supra* note 4.

10. Lisa D. Chew et al., *A Physician Survey of the Effect of Drug Sample Availability on Physicians' Behavior*, 15 J. GEN. INTERNAL MED. 478 (2000); Mary-Margaret Chren & C. Seth Landefeld, *Physicians' Behavior and Their Interactions with Drug Companies A Controlled Study of Physicians Who Requested Additions to a Hospital Drug Formulary*, 271 JAMA 684 (1994); Marilyn Y. Peay & Edmund R. Peay, *The Role of Commercial Sources in the Adoption of a New Drug*, 26 SOC. SCI. MED. 1183 (1988).

11. Michael A. Steinman et al., *Of Principles and Pens: Attitudes and Practices of Medicine Housestaff Toward Pharmaceutical Industry Promotions*, 110 AM. J. MED. 551 (2001).

12. Press Release, PhRMA, PhRMA Adopts New Marketing Code (Apr. 19, 2002), <http://www.phrma.org/mediaroom/press/releases/19.04.2002.390.cfm>.

13. *Gifts to Physicians from Industry*, 265 JAMA 501 (1991); Susan L. Coyle, *Physician-Industry Relations Part 1: Individual Physicians*, 136 ANNALS INTERNAL MED. 396 (2002); Susan L. Coyle, *Physician-Industry Relations Part 2: Organizational Issues*, 136 ANNALS INTERNAL MED. 403 (2002).

advertising is not to be trusted? Modern medical education has promulgated the paradigm of evidence-based medicine.<sup>14</sup> In this model, standards of therapy are derived from hard clinical science in the form of well-designed controlled trials that are sufficiently powered to provide convincing statistical evidence that one treatment is superior to another. In an ideal world, all medical decisions would be based on such evidence. The “winning” drug would be chosen by unbiased clinical trials, and there would be no use for advertising. In this world, physicians would simply prescribe the best drug. So why does this model not work in the real world? To a large degree it is because the U.S. Food and Drug Administration (FDA) typically does not require new drugs to be tested against existing treatments. Instead, it requires only that they be tested against placebos.<sup>15</sup> This is an easier benchmark to meet, as it merely requires that the new drug be effective, but not necessarily better than standard therapy. Drug companies, however, have little financial incentive for head-to-head trials with other effective therapies if they are not required for FDA approval and if one company stands to lose the contest. Thus the controlled trials needed to decide the best therapy are often never performed.

While she argues powerfully, Katharine Greider’s credentials, as well as her scholarship, are skimpy at best. Her terse biosketch on the book cover describes her as a newspaper reporter and free-lance magazine writer with articles focusing on health and medical topics. She lists no footnotes or references anywhere in her book, and her sources are listed in a brief two-page description at the very end. Her book, which runs a mere 180 pages, is published by PublicAffairs, a notable source of alternative and self-acknowledged gadfly journalism.

In contrast, Daniel Vasella, as chairman and chief executive officer of Novartis, one of the largest pharmaceutical companies in the world, has clear-cut qualifications as a business leader in the pharmaceutical industry. He also has a potentially very exciting story to tell in his book, *Magic Cancer Bullet*, published by HarperBusiness. As the subtitle of the book claims, this book sets out to recount “how a tiny orange pill is rewriting medical history.” He provides his personal perspective on the development of the first anticancer therapy which is targeted to a specific molecular lesion. The drug is imatinib (trade name Gleevec), and the disease it treats is chronic myelogenous leukemia (CML). Imatinib is the first commercially

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14. See David L. Sackett et al., *Evidence Based Medicine: What It Is and What It Isn't*, 312 BRIT. MED. J. 71 (1996).

15. Marcia Angell, *The Pharmaceutical Industry — To Whom Is It Accountable?*, 342 NEW ENG. J. MED. 1902 (2000).

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available “molecular” therapy for cancer, and it is designed to inhibit the kinase function of the mutant fusion protein Bcr-Abl that drives the myeloproliferative process underlying the pathogenesis of CML.<sup>16</sup>

Vasella’s book is largely a narrative of Novartis’s involvement in the initial clinical testing of imatinib, an account sprinkled with vignettes about some of the first patients to take the drug. He devotes relatively little time or credit to the years of NIH-funded academic research that made the development of imatinib, and indeed most other modern pharmaceuticals, possible.<sup>17</sup> He describes a number of key scientists in the company who oversaw the synthesis of the compound and the early clinical trials, as well as the anxiety they experienced manufacturing enough of the drug for the anticipated need and monitoring the early reports of clinical testing. Those early trials were dramatically positive, with a large majority of patients with CML showing excellent responses to imatinib, which is a simple oral medication with relatively few side effects.<sup>18</sup> Based on those initial studies, the FDA rapidly approved imatinib for the treatment of CML, and it is now the standard therapy for the stable phase of the disease.<sup>19</sup>

This book is primarily intended to be a “good news” story for patients with leukemia and their families, and not a treatise on public health policy toward the pharmaceutical industry. Nonetheless, Dr. Vasella presents this success story as evidence that large drug companies, driven by the profit motive, are the best hope for the development of effective new therapies. He invokes a business model he calls “innovation management,” a model that “assumes that the private sector is the most capable of carrying out innovative drug discoveries.”<sup>20</sup> This premise is a little difficult to accept in the case of imatinib, given the pioneering work of numerous academic researchers that led to imatinib’s discovery. His arguments for free enterprise, scattered throughout the narrative, are simplistic and underdeveloped: “We must be able to protect our patents for drugs; otherwise there will be no incentive for our scientists to be innovative . . . . And we must structure our prices high enough to assure a return on investment

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16. See VASELLA WITH SLATER, *supra* note 3, at 27.

17. Jeff Gerth & Sheryl G. Stolberg, *Drug Makers Reap Profits on Tax-Backed Research*, N.Y. TIMES, April 23, 2000, at A1.

18. Brian J. Druker et al., *Efficacy and Safety of a Specific Inhibitor of the BCR-ABL Tyrosine Kinase in Chronic Myeloid Leukemia*, 344 NEW ENG. J. MED. 1031-32. (2001).

19. For a discussion of imatinib’s FDA approval process, see VASELLA WITH SLATER, *supra* note 3, at 137-67.

20. VASELLA WITH SLATER, *supra* note 3, at 92.

sufficient to support ongoing research and development.”<sup>21</sup>

Dr. Vasella believes that Novartis took enormous risks to develop imatinib. Unfortunately, however, his view is not well supported by the facts. The effectiveness of imatinib in preclinical tests in cell lines<sup>22</sup> and mouse models<sup>23</sup> of CML was impressive, early clinical trials went very smoothly, and FDA approval took a record-setting two and a half months. He repeatedly sounds the message that he continued to push for the drug’s development, even though he feared the market for it would be too small to make a profit for Novartis, because he thought it was in the best interest of the patients.<sup>24</sup> While these are noble sentiments, they ring a little false when one recognizes that imatinib has significant activity in three other rare malignancies—gastrointestinal stromal tumors (or GISTs),<sup>25</sup> hypereosinophilic syndrome,<sup>26</sup> and certain forms of chronic myelomonocytic leukemia,<sup>27</sup> and is now being tested in a variety of common tumors, such as prostate cancer.<sup>28</sup> Gleevec has also helped establish Novartis as one of the premier oncology franchises leading the targeted therapy drive of the future. So Gleevec may yet make money for Novartis.

The last chapter of the book, cleverly entitled “Success Management,” is largely devoted to justifying the pricing and patent practices of the pharmaceutical industry. Vasella talks in fair detail about the pricing issues for Gleevec, citing an unreferenced claim that the average cost of research and development for a new drug is about \$880,000,000.<sup>29</sup> Other authors have put the figure closer to \$500,000,000.<sup>30</sup> He provides no figures for the

21. *Id.* at 18.

22. Brian J. Druker et al., *Effects of a Selective Inhibitor of the Abl Tyrosine Kinase on the Growth of Bcr-Abl Positive Cells*, 2 NATURE MED. 561 (1996).

23. Nicholas C. Wolff & Robert L. Ilaria, Jr., *Establishment of a Murine Model for Therapy-Treated Chronic Myelogenous Leukemia Using the Tyrosine Kinase Inhibitor STI571*, 98 BLOOD 2808 (2001).

24. *See, e.g.*, VASELLA WITH SLATER, *supra* note 3, at 15-16.

25. Heikki Joensuu et al., *Management of Malignant Gastrointestinal Stroma Tumours*, 3 LANCET ONCOLOGY 655 (2002).

26. Jan Cools et al., *A Tyrosine Kinase Created by Fusion of the PDGFRA and FIP1L1 Genes as a Therapeutic Target of Imatinib in Idiopathic Hypereosinophilic Syndrome*, 348 NEW ENGLAND J. MED. 1201 (2003).

27. Magnus K. Magnusson et al., *Activity of STI571 in Chronic Myelomonocytic Leukemia with a Platelet-Derived Growth Factor Beta Receptor Fusion Oncogene*, 100 BLOOD 1088 (2002).

28. VASELLA WITH SLATER, *supra* note 3, at 27-28.

29. VASELLA WITH SLATER, *supra* note 3, at 175.

30. Davidoff, *supra* note 4.



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research and development dollars expended by Novartis to develop imatinib itself, and states that they based their pricing for Gleevec (\$2,200/month) on the cost of alpha interferon, another standard drug used to treat CML.<sup>31</sup> My Veterans Affairs hospital pays \$1,432 for a month's supply of imatinib; by comparison, hydroxyurea, another oral medication used to control CML, costs less than \$20/month.<sup>32</sup> Vasella quite correctly points out the inequities in Medicare reimbursement that preclude payment for oral cancer drugs and force many elderly patients with CML to pay for their medication out of their own pockets.<sup>33</sup> This Medicare policy will seem increasingly dated as more molecular therapies are introduced, replacing toxic intravenous medications with simpler oral therapies with fewer side effects. While Vasella and Novartis should be applauded for initiating a patient support program for those individuals who cannot afford the medication,<sup>34</sup> several other pharmaceutical companies already have similar policies for expensive cancer medications.<sup>35</sup>

Reading these two books back to back is reminiscent of the old saw about the statistician who would say that a person with one foot in a bucket of ice water and the other foot in a bucket of boiling water was, on average, comfortable. Read together the books do not provide a balanced perspective on the problems of the pharmaceutical industry, nor any guidance as to how change could best be effected. As of this writing, President Bush had just signed a Medicare prescription drug benefit into law,<sup>36</sup> but its value to consumers is delayed and remains uncertain. Until there is an effective national health policy for prescription drugs, the licensed health care providers who can prescribe expensive life-saving medications represent the most effective agents for near-term change. These providers need to find the will to 1) pressure drug companies to

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31. VASELLA WITH SLATER, *supra* note 3, at 179.

32. Information regarding spending at the author's Veterans Affairs hospital is on file with the author. For information about the pricing of hydroxyurea, see *Hydroxyurea, DestinationRx, at* <http://www.destinationrx.com/prescriptions/refine.asp?BrandName=Hydroxyurea> (last visited Jan. 8, 2004).

33. VASELLA WITH SLATER, *supra* note 3, at 126.

34. *Id.* at 179.

35. For a list of other pharmaceutical companies providing such programs, see *Indigent Patient Programs*, The Nutrition Advisor, *at* <http://www.nutritionadvisor.com/indigent.htm?source=overture#research> (last visited Jan. 16, 2004).

36. Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Pub. L. No. 108-173, 117 Stat. 2066.

reduce or eliminate Direct-To-Consumer advertising, 2) resist the aggressive marketing practices directed at them, 3) use evidence-based medicine wherever possible to assure more cost-effective (and cost-saving) prescribing, and 4) press Congress to pass legislation requiring comparative drug trials before FDA licensing.<sup>37</sup>

If marketing practices are to be reduced substantially, those marketing practices must be made to fail. For health care professionals who need more moral support to take on these challenges, they would do well to go to the website of the non-profit group No Free Lunch,<sup>38</sup> a devoted group of physicians endeavoring to limit the influence of pharmaceutical marketing on prescribing practices. At that website, physicians and medical students can get concrete suggestions on actions they can take to aid in that endeavor and are invited to take the following public pledge: "I . . . pledge to accept no money, gifts, or hospitality from the pharmaceutical industry; to seek unbiased sources of information and not rely on information disseminated by drug companies; and to avoid conflicts of interest in my practice, teaching, and/or research."<sup>39</sup> Neither Greider nor Vasella discuss the important role that physicians could play in the near term in creating change in pharmaceutical pricing. To paraphrase the closing comment in Greider's book, if the perspective of a large drug company is "*Who is going to stop me?*"<sup>40</sup> physicians must say "*We will.*"

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37. Angell, *supra* note 15.

38. *Just Say No to Drug Reps*, No Free Lunch, at <http://www.nofreelunch.org/> (last visited Jan. 6, 2004). The website invites readers to protest drug-company sponsored meals to their Department Chairs and/or Program Directors and to give talks on the subject of drug-company influence on prescribing practices, using slide show presentations created by No Free Lunch. *What Can You Do?*, No Free Lunch, at <http://www.nofreelunch.org/todo.htm> (last visited Jan. 6, 2004).

39. *Take the Pledge*, No Free Lunch, at <https://ironclad.secure-orders.net/nofreelu/pledge.htm> (last visited Jan. 6, 2004).

40. GREIDER, *supra* note 1, at 174.