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BOOK REVIEW:

OVERDOSE: HOW EXCESSIVE GOVERNMENT REGULATION STIFLES PHARMACEUTICAL INNOVATION

Authored By: *Richard A. Epstein**

Overdose offers a comprehensive examination of the pharmaceutical industry by following the course of a new drug as it progresses from early development to final delivery. Richard A. Epstein looks closely at the regulatory framework that surrounds creating pharmaceutical products, and Epstein assesses which current legal and regulatory practices work and which ones have gone awry. In *Overdose* Epstein cautions that more stringent controls over every aspect of drug development and approval will stifle pharmaceutical innovation and slow delivery of beneficial treatments to patients who need them. Epstein considers the numerous challenges that face the industry and argues that to ensure continuing creativity, efficiency and success of the pharmaceutical industry, the best system will feature strong property rights and clear enforceable contracts with minimal regulatory or judicial interference.

Reviewed By: *John E. Calfee, Ph.D***

Written by a prolific and accomplished legal scholar, Richard Epstein's *Overdose* evolved from a collection of occasional writings into a monograph. It retains the characteristics of a hastily written product of a careful and adventurous thinker who happens to compose fluid, sometimes colorful, prose. The book is full of insights. It gives disproportionate emphasis to topics the author knows well (such as intellectual property and products liability law) with scant mention of ones he has had no occasion to visit (the design and regulation of clinical trials, and the nuts and bolts of price controls, to name two essential topics). The subtitle for the book's tendentious title is a bit misleading. Roughly half the book passes before Epstein reaches the topics that most people associate with pharmaceutical industry regulation: price controls and especially, the Food and Drug Administration (FDA). However, Epstein sees all of his main topics, starting with intellectual property and ending with tort liability

litigation, as describing a series of “regulatory hurdles” that useful pharmaceuticals must surmount.

Epstein is a classical liberal whose formidable analytical skills are often harnessed to the cause of minimal government intervention (*Simple Rules for a Complex World; Skepticism and Freedom: A Modern Case for Classical Liberalism*). Many of his arguments are highly nuanced rather than doctrinaire and, especially on intellectual property, are less predictable than one might expect. What we get is a very practical form of libertarianism arguing that concrete results confirm the validity of basic principles. Virtually the entire work is suffused with economic reasoning although careful parsing of the law (on deceptive marketing, for example) sometimes leaves economics in the background. Much of this reasoning starts with the most fundamental economic characteristic of the pharmaceutical market, which is the huge gap between prices and marginal costs.

The result is a work to be reckoned with. Anti-pharmaceutical-industry books published in the past few years have been common and there is no let-up in sight.¹ Epstein’s monograph is a rare example of an opposing point of view. He tackles nearly every major argument raised in this increasingly crowded field of conflict. He also addresses topics that have yet to capture public attention but may do so, such as proposals for government buyouts of patents and overt government competition with private industry to bring new drugs to market.

I. INTELLECTUAL PROPERTY

Overdose begins with property law, but with Roman property law rather than intellectual property law as one might expect. Epstein emphasizes that patents and other forms of intellectual property are

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¹ Leading examples include MARCIA ANGELL, *THE TRUTH ABOUT THE DRUG COMPANIES: HOW THEY DECEIVE US AND WHAT TO DO ABOUT IT* (Random House 2004); JERRY AVORN, *POWERFUL MEDICINES: THE BENEFITS, RISKS, AND COSTS OF PRESCRIPTION DRUGS* (Knopf 2004); PHILIP J. HILTS, *PROTECTING AMERICA’S HEALTH: THE FDA, BUSINESS, AND ONE HUNDRED YEARS OF REGULATION* (Univ. of N. Carolina Press 2004); JEROME KASSIRER, *ON THE TAKE: HOW MEDICINE’S COMPLICITY WITH BIG BUSINESS CAN ENDANGER YOUR HEALTH* (Oxford University Press 2004).

relatively recent legal inventions. A lawyer-economist to the core, he explains why intellectual property rights made little economic sense in earlier eras. Then he proceeds to explain why patents, in particular, are essential to drug development, an industry barely a century old. Throughout, economic incentives are at the core of the evolution of I.P. law, which Epstein believes proceeded in a largely logical and beneficial fashion. The entire discussion is enlightening, with an emphasis on gradualism (starting, of course, with the default situation of no I.P. whatsoever) and learn-by-doing as patent protection expanded to encompass forms of life, snippets of DNA, and biological mechanisms that serve as drug targets. He explains why a “thicket” of biology-based patents could create an “anticommons” that would inhibit progress built on the accumulation of knowledge, and then cites evidence that, at least so far, there is little to worry about in this respect. An especially difficult topic is research tools, where various sectors of pharmaceutical and other high-tech industries disagree among themselves regarding the appropriate rules for commercial use. In *Duke Univ. v. Madey*,² the Supreme Court seems to have struck a reasonable balance, at least for the time being, between fair use of research tools in purely academic research versus commercially-oriented research conducted by academic institutions such as universities.

That Epstein sees patents as the essential source of new drug development is no surprise. But he is suspicious of broad patents, a point on which, again, the pharmaceutical industry is often split. He emphasizes the diverse interests that competitors have in the substance and scope of what is permitted in granting patents. For him, the default option is to make patents as narrow as possible. He is also surprisingly cool toward the 1980 Bayh-Dole Act,³ which permits recipients of National Institutes of Health (NIH) research support to patent what they discover. On this tricky issue, Epstein’s analysis is a model of economic reasoning, starting with first principles and reaching intriguing implications for contemporary issues.

Epstein then offers a superb analysis of two proposals that have received relatively little attention but will almost certainly receive more as the political debate over the pharmaceutical industry continues to mount. Chapter Nine looks at proposals for government buyouts of pharmaceutical patents. Such proposals arise from the wide disparity between prices and marginal costs and the social costs of such

² *Duke Univ. v. Madey*, 539 U.S. 958 (2003).

³ Bayh-Dole Act, 35 U.S.C. §§ 200-212 (1980).

arrangements, namely, the inability to attain prices that are efficient both from the standpoint of distribution (where marginal-cost pricing would allow usage by everyone who finds the benefits exceed costs) and research incentives (where the expectation of supra-marginal-cost pricing is essential to motivate investment). Epstein explains the common observation that firms already have incentives to discriminate among users to charge lower prices where willingness to pay is relatively small, while acknowledging the natural limits to price discrimination in a market where arbitrage is hard to stop. Epstein also adds interesting and subtle arguments to the effect that government buyouts are simply not practical. They would run aground on the bewildering variety of pricing and risk-taking problems that competitive markets solve in an equally bewildering mix of market transactions.

Chapter Ten is on the “Socialization” of drug development, by which he means proposals to encourage government agencies, most prominently the (NIH), to enter the drug development market in competition with private firms. Epstein argues that government agencies have no mechanism for solving the intricate problems of investing in high-stakes, high-risk research. Again, the arguments are remarkably subtle and compelling for someone with limited formal training in economics.

One point Epstein does not touch upon is what we can learn from the fact that substantial areas of drug development already exist where private market incentives are known to be weak or absent. These extend well beyond the much despaired failure to develop new treatments and preventatives for tuberculosis, malaria, and other tropical diseases, to such rich-nation plagues as drug-resistant antibiotics and the failure to research new uses of off-patent drugs. The eclipse of research incentives with patent expiration is obvious and explains the lack of industry research on, for example, unlabeled uses for Neurontin, an epilepsy drug whose greatest value probably lies in treating neuropathic pain.⁴ Antibiotics are different. The specter of drug resistance causes physicians, for the best possible reasons, to use a newly approved antibiotic as little as possible in order to keep it in reserve for when older drugs encounter widespread resistance. The result is limited sales during the years before patent expiration. The adverse impact on incentives to develop new classes of antibiotics

⁴ Robert H. Dworkin, et al. *Advances in Neuropathic Pain: Diagnosis, Mechanisms, and Treatment Recommendations*, 60 ARCHIVES OF NEUROLOGY 1524, 1524-34 (2003).

(which are notoriously difficult to create anyway) have been much discussed.⁵ Nonetheless, NIH has failed to step in. We still rely upon the private sector for the very few innovative antibiotics that do get developed. This peculiar dynamic reinforces Epstein's arguments about the futility of relying upon publicly supported drug development in place of private sector research.

Epstein does not address one point, which in fact is relatively unexplored despite its importance. The relationship between basic research and successful branded pharmaceuticals is far from a one-sided one in which industry realizes gains from publicly supported research. Many of the top-selling drugs actually contribute to basic research by serving as tools for rejecting otherwise unresolved hypotheses that in some cases are quite fundamental. An example is how clinical trial results from the increasing potent statin class of cholesterol-reducing drugs has transformed understanding of both the role of low-density lipoprotein cholesterol (LDL cholesterol) in cardiovascular disease and the cause of heart attacks.⁶

II. PRICES AND PRICE CONTROLS

All advanced nations except the United States control patented drug prices through legislation. Proposals to do so in the U.S. are common, including "reimportation" (actually, just importation, since most of the drugs are not manufactured in the U.S.) from foreign nations at controlled prices, forcing firms to sell in the U.S. at prices they charge elsewhere, and expanding the ambit of price controls where they exist in the U.S., such as at the Veterans Administration. Epstein's analyses of price controls start with patents and their chief effect, monopoly pricing at levels far above manufacturing costs. His detailed analysis of recent proposals is somewhat dated in the rapidly changing political environment, but the basic arguments are still quite sound. He is particularly sharp on Constitutional arguments, drawing on his work on the takings clause.⁷ The essential point, however, is that price controls

⁵ Allison E. Aiello, Nicholas B. King, and B. Foxman, *Ethical Conflicts in Public Health Research and Practice; Antimicrobial Resistance and the Ethics of Drug Development*, 96 AM. J. PUBLIC HEALTH 1910, 1910-14 (2006).

⁶ Eric Topol, *Intensive Statin Therapy: A Sea Change in Cardiovascular Prevention*, 350 NEW ENG. J. MED. 1562, 1562-64 (2004); Daniel Steinberg, *An Interpretive History of the Cholesterol Controversy, Part V: The discovery of the statins and the end of the controversy*, 47 JOURNAL OF LIPID RESEARCH 1339, 1339-51 (2006).

⁷ RICHARD A. EPSTEIN, *TAKINGS: PRIVATE PROPERTY AND THE POWER OF EMINENT DOMAIN* (Harvard Univ. Press 1985).

are bound to undermine research incentives, and he cites recent economic estimates of the effects of pushing U.S. prices down to European levels.

Epstein has almost nothing to say about how foreign price controls actually work, which is understandable given the diversity of those mechanisms. He also does not mention the remarkable fact that foreign price controls are largely ineffective against sole-source biotechnology drugs such as targeted drugs for cancer and rheumatoid arthritis.⁸

III. FDA REGULATION

FDA regulation of pharmaceuticals is a much-analyzed topic to which Epstein has less to add than to other matters addressed in this book. His starting point is the familiar disparity between the excessive weight given by FDA staff to Type I errors (the approval of a new drug that turns out badly) compared to Type II errors (failing to approve a useful drug). The disparity in weights arises from external forces. Type I errors become public, whereas Type II errors are observed mainly by insiders. Epstein agrees with many economists that the FDA operates with excessive caution, giving far too much weight to safety when reviewing new drugs and therefore delaying or preventing valuable drugs from reaching desperately sick patients. His solution is not reform, but privatization. Citing Henry Miller, he recommends that the drug approval system should be changed along the lines of medical device approvals in the European Union, where private “notified bodies” compete to review and approve new and altered medical devices.⁹ Chai provides fascinating details about the very different European and American systems for medical device regulation.¹⁰

An essential factor in recent FDA behavior is only alluded to by Epstein. Ever since Merck withdrew its pain reliever Vioxx in September 2004 because of cardiovascular risks, the FDA has endured years of truly vitriolic criticism from leading medical journals,

⁸ John E. Calfee & Elizabeth DuPré, *The Emerging Market Dynamics of Targeted Therapeutics*, 25 HEALTH AFFAIRS 1302, 1302-08 (2006).

⁹ HENRY I. MILLER, *TO AMERICA'S HEALTH: A PROPOSAL TO REFORM THE FOOD AND DRUG ADMINISTRATION* (Hoover Institution Press 2000).

¹⁰ John Y. Chai, *Medical Device Regulation in the United States and the European Union: a Comparative Study*, 55 FOOD DRUG L. J. 57, 57-80 (2000).

Congress, and the news media.¹¹ On the whole, the FDA's performance in the Vioxx affair has been sound.¹² This is clear from, among other things, the recommendations of American and Canadian expert panels to keep Celebrex, the drug most similar to Vioxx, on the market and even to bring Vioxx back,¹³ plus the fact that advanced nations with regulatory apparatus comparable to the FDA have not only kept Celebrex on the market but have approved Arcoxia, a drug similar to Vioxx that was also developed by Merck.¹⁴ Nonetheless, the criticism has been unrelenting, reinforced by a highly critical Institute of Medicine (IOM) report on FDA oversight of drug safety.¹⁵ In historical terms, however, this is merely an especially vivid example of the forces that cause the FDA to be excessively cautious in approving new drugs. The impact of the Vioxx episode and its aftermath became very clear in April 2007 when an FDA advisory committee, prodded by the FDA itself, voted twenty to one against approving a new member of the Cox-2-inhibitor class (of which Vioxx was one) on the grounds that proof that the it was as safe and effective as the drugs against which it would compete was insufficient reason to permit the drug on the market.¹⁶

IV. MARKETING

Epstein's discussion of pharmaceutical marketing is among his most forcefully argued sections and is likely to arouse strong dissent from the industry's critics. The starting point, again, is the yawning gap between prices and marginal costs. The implication is that once a drug has traversed the approval process and is available for use, the task of

¹¹ E.g., Richard Horton, *Vioxx, the Implosion of Merck, and Aftershocks at the FDA*, 364 THE LANCET 1995, 1996 (2004); Eric J. Topol, *Failing the Public Health: Rofecoxib, Merck, and the FDA*, 351 NEW ENG. J. MED. 1707, 1707-09 (2004).

¹² John E. Calfee, *The Vioxx Fallout*, AEI HEALTH POLICY OUTLOOK (Sept.- Oct. 2005).

¹³ Susan Okie, *Raising the Safety Bar: the FDA's Coxib Meeting*, 352 NEW ENG. J. MED. 1283, 1283-85 (2005); Health Canada, *Report of the expert advisory panel on the safety of Cox-2 selective NSAIDs*, July 8, 2005, available at http://www.hc-sc.gc.ca/dhp-mps/prodpharma/activit/sci-consult/cox2/sap_report_gcs_rapport_cox2_e.html (last visited April 24, 2007); the latter is cited by Epstein.

¹⁴ Calfee, *supra* note 12; Anna Wilde Mathews, *FDA Panel's Vote Against Arcoxia Gives Merck New Headache in Painkiller Class*, WALL STREET JOURNAL, Apr. 13, 2007, at A3.

¹⁵ Institute of Medicine, *The Future of Drug Safety: Promoting and Protecting the Health of the Public* (National Academy of Sciences 2006).

¹⁶ Mathews, *supra* note 14.

getting that drug to the right users is fraught with difficulty but also with large payoffs in terms of both profits and health. Essentially, Epstein makes several arguments. One is that marketing is, paradoxically, the source of reasonable pricing. Good marketing will increase sales, perhaps dramatically, thus spreading development costs (which in the long run will determine prices) across more customers at lower individual prices. Marketing is also essential to patient welfare, partly by getting new drugs to the patients who would benefit the most. Finally, because it increases expected payoffs from innovative new drug development, marketing bolsters R&D investment.

This is largely a conceptual treatment, however, supplemented by tedious (for the non-lawyer, at least) explication of deceptive advertising law. Epstein only glances at the extensive and compelling medical literature on under-diagnosis and under-treatment of conditions amenable to drug treatment. Although he does not mention it, there is also a burgeoning literature employing survey and econometric methods to assess direct-to-consumer advertising of prescription drugs. That literature provides considerable support for Epstein's conclusion that pharmaceutical marketing works to the benefit of patients, although the effects are probably modest, as is the total volume of advertising.¹⁷

V. TORT LIABILITY

Epstein devotes the final section of his book to tort liability, one of his specialties. He begins by deploring the eclipse of contracts as a way to modify tort law. Much of the discussion focuses on the ongoing litigation over Vioxx. Epstein sees serious problems with every aspect of the typical plaintiff's case starting with simple facts (was Vioxx even prescribed?) and proceeding through the details of clinical trials, FDA proceedings, and much more including a strange but instructive episode involving the renowned *New England Journal of Medicine* and its public relations firm.

¹⁷ John E. Calfee, *What Do We Know About Direct-To-Consumer Advertising Of Prescription Drugs?*, HEALTH AFFAIRS, 116, 119 (web exclusive) (last visited April 24, 2007); Ernst R. Berndt, *The United States Experience with Direct-to-Consumer Advertising of Prescription Drugs: What Have We Learned?*; paper presented at the International Conference on Pharmaceutical Innovation, Taipei, Taiwan, May 26-27, 2005. Forthcoming in FRANK A. SLOAN AND CHEE-RUEY HSIEH, *PROMOTING AND COPING WITH PHARMACEUTICAL INNOVATION: AN INTERNATIONAL PERSPECTIVE* (Cambridge University Press late 2006).

Epstein concludes that the liability system is incapable of efficiently handling either Vioxx litigation, in particular, or pharmaceutical liability litigation in general. Juries, for example, cannot reasonably decide fiendishly scientific issues. Damages' payments, especially pain and suffering compensation and punitive damages, will fatally distort the incentives of all parties including drug development firms. He is especially opposed to liability for design defects, which amounts to a second drug approval system built on top of the official system run by the FDA. The result is to reinforce the excessive caution already built into FDA deliberations.

Epstein therefore advocates reforms of the products liability system. These include the restoration of contract (presumably a hopeless cause), pre-emption of state tort law by FDA findings on the balance of safety and efficacy and on risk disclosure, some sort of no-fault compensation that would cap pain and suffering awards, and a system of fines instead of litigation for genuinely reckless behavior by pharmaceutical firms.

VI. THE BOOK AS A WHOLE

Epstein constructed his monograph around an immense intellectual superstructure. This yields both advantages and disadvantages. One disadvantage is that obviously important topics are raised but barely touched despite a thriving academic literature on which to draw. Examples include drug cost-effectiveness, the operations of price controls (mainly in foreign nations), the development of clinical biomarkers, and the redesign of clinical trials to facilitate drug development and approvals in the wake of rapid technological change.

But the advantages of Epstein's ambitious approach are considerable. Although one might expect the plenitude of topics arising from the book's superstructure to prove hopelessly confusing, the paradoxical effect is to facilitate understanding of why things work the way they do and why it would be dangerous to make drastic changes to patent law and laws about prices, to name two examples. Yes, the interactions among so many thorny topics are too subtle and complicated to delineate fully satisfactorily; but, they reflect the obdurate nature of the system in which pharmaceutical development takes place, and they serve as notice of both the dangers of precipitous change and the potential gains from well-conceived reform. Thus some of the most interesting and provocative chapters are not on FDA regulation or torts, but on intellectual property, government buy-outs of

pharmaceutical patents, and direct government drug development. All these and more are addressed through subtle and illuminating economic reasoning. As a whole, the book's arguments are cogent and compelling. There is much to command the attention of anyone concerned with public policy and the pharmaceutical industry.