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# An Information Prescription for Prescription Drug Regulation

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# An Information Prescription for Drug Regulation

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## INTRODUCTION

When “safe and effective” joined the Food Drug Cosmetic Act as a criterion for the sale of new prescription drugs in 1962,<sup>1</sup> the statute empowered the Food and Drug Administration (FDA) to withhold every new pharmaceutical product from the market until its seller, in its application for FDA approval, demonstrated favorable future conditions. Sellers since 1962 have had to show that their new drug will not poison people who take it into their bodies,<sup>2</sup> and that they will deliver on the promise in its label.<sup>3</sup> Whenever this applicant-seller cannot demonstrate safety and effectiveness, the FDA cannot approve its drug. Without FDA approval, a drug cannot be sold in interstate commerce.

Through this statutory language, lack of safety and lack of effectiveness became the genre of adversity that pharmaceutical regulation, as a species of regulation in general, anticipates and strives to control. Draft rules

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1. Drug Amendments of 1962, Pub. L. No. 87-781, 76 Stat. 780 (1962) (codified as amended at 21 U.S.C. § 355 et. seq. (2000)).

2. This paraphrase of “safe” is controversial, as we discuss below, *passim*.

3. One drug-law scholar uses legislative history to demonstrate that the meaning of “effective” is what Congress intended, and that Congress rejected efficacious, or bearing the quality of “efficacy,” which refers to clinical improvement. Jennifer Kulynych, *Will FDA Relinquish the “Gold Standard” for New Drug Approval? Redefining “Substantial Evidence” in the FDA Modernization Act of 1997*, 54 FOOD & DRUG L.J. 127, 129, 132-34 (1999).

published daily in the Federal Register aim to reduce polluted air, choking-hazard toys, dirty groundwater, hazardous materials, toxic pesticides, invidious discrimination, undisclosed risks in securities offerings, eighteen hour workdays, and other dangers in the parade of regulated-against horribles. Lack of safety and lack of effectiveness are the relevant horribles here. Like other regulated sectors, this industry must exert itself to reduce the adversities that its business is wont to create.

Does "safe and effective" mean something beyond the usual regulatory reference to externalities? "Safe" does not equal "incapable of doing harm": all drugs do harm.<sup>4</sup> On the question of what the word safe *does* mean, the amended Food Drug Cosmetic Act makes what we argue was the only possible choice: in Section 505, where a definition would go, Congress demurred on defining. To borrow a riff of about the same age as the drug amendments, regulators evidently will know safety when they see it.<sup>5</sup> "Effective," though not exactly defined in the 1962 update that introduced the requirement of demonstrated effectiveness, comes with a bit more content: Congress took pains to require "substantial evidence" of effectiveness before the FDA may approve a new drug,<sup>6</sup> and has elaborated on what constitutes substantial evidence.<sup>7</sup> In rejecting a near-synonym, "efficacy," Congress apparently also declined to require that

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4. "All substances are poisons; there is none which is not a poison. The right dose differentiates a poison . . ." CASARETT & DOULL'S TOXICOLOGY: THE BASIC SCIENCE OF POISONS 4 (Curtis D. Klaassen et al. eds., 5th ed. 1996).

5. Justice Potter Stewart, on obscenity: "I shall not today attempt further to define the kinds of material I understand to be embraced within that shorthand description; and perhaps I could never succeed in intelligibly doing so. But I know it when I see it . . ." *Jacobellis v. Ohio*, 378 U.S. 184, 197 (1964) (Stewart, J., concurring).

6. For most drugs the FDA requires findings in two controlled studies that the drug outperforms a placebo in causing the human clinical changes that its maker promises to achieve. Under rare circumstances, one controlled study will suffice. See 21 U.S.C. § 355(d) (2000) ("If the Secretary determines, based on relevant science, that data from one adequate and well-controlled clinical investigation and confirmatory evidence (obtained prior to or after such investigation) are sufficient to establish effectiveness, the Secretary may consider such data and evidence to constitute substantial evidence for purposes of the preceding sentence.").

7. "Effective" creates a regulatory expectation of other evidence, such as animal-studies results, to demonstrate the capacity of a drug. Further detail on what effectiveness demands is codified at 21 U.S.C. § 355(d).

a drug cause clinical improvement in a patient's condition. "Effective," as was mentioned, refers to the obligation to deliver on the promises of a label.

The adjectives hold a distinct linguistic status that affects their function in statutory and regulatory law. Because safe and effective are both what linguists call gradable adjectives, a speaker of English can add an adverb and say "very effective" or "more safe."<sup>8</sup> Better suited to binary yes-no regulation are absolute adjectives, including minimum-standard adjectives ("wet" or "impure") and maximum-standard adjectives ("dry" or "pure"). Even more suited to binary regulation among the absolute adjectives are noncomparatives like "wooden" and "locked."<sup>9</sup> Being able to say "very" (or "partially," "insufficiently," "unambiguously," and so on) "safe" or "effective" in a language where the phrase "very handmade" would be absurd suggests the need for flexibility, nuance, and context in fulfilling the mandate of Section 505 of the Food Drug Cosmetic Act. Exploring this flexible mandate, while hewing as closely as possible to "safe and effective," we claim in this Essay that prescription drugs are different from other commodities and activities subject to federal regulation. We identify five overlapping aspects of this difference.

First, this industry is virtually unique in its pursuit of the same thing that its overseeing agency demands. Regulation in other sectors points at the dark underbelly of a business. You think you produce coal; regulators say you produce acid rain. You're trying to sell stock; regulators worry you are unloading hidden risks to investors. Your punch press on the shop floor creates finished goods—and amputations. In the prescription drugs business, however,

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8. See Christopher Kennedy, *Vagueness and Grammar: The Semantics of Relative and Absolute Gradable Predicates*, June 25, 2005, <http://www.semanticsarchive.net> (last visited Jan. 30, 2005).

9. *Id.* For examples of absolute non-comparative adjectives in the Code of Federal Regulations, see 9 C.F.R. § 114.6 (2006) ("Each *biological* product, when in *liquid* form, shall be mixed thoroughly in a *single* container.") (emphasis added); 49 C.F.R. § 40.131 (2005) ("When, as the MRO [medical review officer], you receive a *confirmed* positive, *adulterated*, *substituted*, or *invalid* test result from the laboratory, you must contact the employee directly (i.e., actually talk to the employee), on a *confidential* basis, to determine whether the employee wants to discuss the test result.") (emphasis added).

regulators and regulated claim to seek safe and effective drugs, at least in their rhetoric. In this Essay, we recognize that the industry's many critics might retort that what the industry wants is no more than profit.<sup>10</sup> To sidestep a needless quarrel, here we comment only on the reputation the industry seeks rather than try to establish sincerity.<sup>11</sup> For those who seek to market prescription drugs, a "safe and effective" product, or perhaps "public health," is both the regulatory mission they must obey and the ostensible good they try to sell. By contrast, resource extractors like mining businesses seldom claim to pursue pollution reduction as a chief goal. Securities underwriters do not say they make a living selling disclosure.

The closely related second point is that in this sector, too much regulatory suppression leads to the same ill effects as too little. Safety concerns, for example, can be defeated by both overregulation and underregulation: approving a risky drug harms patients who use it and suffer its side effects; declining to approve a risky drug will keep it from patients who would benefit from what the drug could do to fight their condition. The effectiveness criterion also can make paired-set errors. On the underregulation side of the ledger, patients can die from having spent time and energy on a useless nostrum;<sup>12</sup> on the overregulation side, a drug that would be helpful to a number of patients can flunk controlled studies and never reach those needy

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10. At one of the workshop presentations of this Essay, a participant argued that the drug industry would "sell water" if it could. For book-length criticism of this sector published in one year alone, see JOHN ABRAMSON, *OVERDOSED AMERICA: THE BROKEN PROMISE OF AMERICAN MEDICINE* (2004); MARCIA ANGELL, *THE TRUTH ABOUT THE DRUG COMPANIES: HOW THEY DECEIVE US AND WHAT TO DO ABOUT IT* (2004); JERRY AVORN, *POWERFUL MEDICINES: THE BENEFITS, RISKS, AND COSTS OF PRESCRIPTION DRUGS* (2004); MERRILL GOOZNER, *THE \$800 MILLION PILL: THE TRUTH BEHIND THE COST OF NEW DRUGS* (2004).

11. For examples of pharmaceutical-company public statements claiming a stake in public health, see <http://www.pfizerpublichealth.com> (last visited Aug. 8, 2006); Schering-Plough, *Who We Are*, [http://www.schering-plough.com/schering\\_plough/about/about.jsp](http://www.schering-plough.com/schering_plough/about/about.jsp) (stating that "we aspire to earn the trust of doctors, patients and customers by providing a steady flow of innovative, science-based medicines and services that improve the health and well-being of people around the world.") (last visited Aug. 8, 2006).

12. See *United States v. Rutherford*, 442 U.S. 544, 556-58 (1979) (refusing to allow an exception to the effectiveness requirement for terminal patients for this reason).

consumers.<sup>13</sup> Here drugs present another contrast to most industries, where too much regulation will cause ill effects that are different from, rather than similar to, the ill effects of too little regulation.

Third, whereas regulation in other industries seeks to minimize harmful effects, regulation of prescription drugs has a subtler task: to achieve balance between safety (that is, relatively few harmful effects) and effectiveness (understood as enough clinical potency to deliver on the manufacturer's promise). The adjective "safe" in the Food Drug Cosmetic Act can be understood only in a context of potential benefits.<sup>14</sup> Regulators tolerate grim side effects in a lifesaving drug that would be fatal to the approval of a drug with superficial and cosmetic effects, or for yet another beta blocker.

In other words, drug regulation seeks to maximize *utility* to consumers, rather than protect them from discrete dangers in the mode of ordinary regulation—and utility is in a sense the sum of safety and effectiveness.<sup>15</sup> A strong

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13. Effectiveness is the more controversial of the two criteria. Daniel B. Klein and Alexander Tabarrok, for example, post critical writings on their website, *FDA Review*. See <http://www.fdareview.org> (last visited Feb. 18, 2006). Relying on work by Sam Peltzman and Steven Wiggins, Klein and Tabarrok argue that the effectiveness criterion has kept valuable therapies off the market and thereby caused "tens of thousands of excess deaths." See Daniel B. Klein & Alexander Tabarrok, *Who Certifies Off-Label?*, REGULATION MAGAZINE, Summer 2004, at 60, 63 [hereinafter Klein & Tabarrok, *Who Certifies*].

14. The director of the FDA's Center for Drug Evaluation and Research made this point in a 1999 interview:

If I say to you, 'you have a 1 in 100 chance of dying from this drug, but it will do wonderful things for you,' that might mean something totally different to you than it would to me. So we need to bring patients, as well as those who treat patients, in much more and ask them, 'What is an acceptable risk?'

Tamar Nordenberg, *When Is a Medical Product Too Risky?*, FDA CONSUMER, Sept.-Oct. 1999, at 8, 11, available at [http://www.fda.gov/fdac/features/1999/599\\_med.html](http://www.fda.gov/fdac/features/1999/599_med.html) [hereinafter *Woodcock Interview*].

15. Effectiveness might be understood to include cost-effectiveness. For a summary of drug utility that implicitly includes this value, written to help guide third-party payors, see *Format for Formulary Submissions—A Brief Description*, available at <http://www.fmcpcnet.org> [hereinafter *Format for Formulary Submissions*].

The *Format* is a set of guidelines, a template that drug companies can use to prepare submissions of new and existing pharmaceuticals for a health system's Pharmacy and Therapeutics (P & T) Committee.

showing in one encourages drug regulators to tolerate a weaker showing in the other. For example, federal regulatory law allows animal studies alone to suffice preliminarily for a finding of effectiveness when a new drug is "intended to treat life-threatening and severely debilitating illnesses" to which "no satisfactory alternative therapy exists," or offers a therapy for which human efficacy studies are not ethical or feasible.<sup>16</sup> The aforementioned grim side effects (that is, lack of safety) are a price worth paying only for a drug that can do much good (or, in other words, is extremely effective). A feeble drug—one that is not too effective—warrants approval only when it is extraordinarily safe.

A fourth difference between prescription-drug regulation and other regulation lies in its distinct and separate target audiences. To be sure, most regulation strives to protect more than one cohort. Environmental rules governing asbestos removal, for example, might have in mind abatement workers, people located inside buildings, and real estate holders, among other sectors. But divergences are much sharper in the industry we address here. Who are its consumers? When the last comprehensive amendments to the Food Drug Cosmetic Act were enacted in 1962, the answer was simple: physicians. Manufacturers did not market prescription drugs to patients then,<sup>17</sup> and

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Manufacturers who follow these guidelines generate a standardized set of clinical and economic evidence, providing health systems with a broad and more accurate analysis of a drug's impact on a patient. As a result, health plans can more confidently answer the question: 'Which drugs offer the greatest opportunity to improve patient health at reasonable costs, thus providing good value?' Previously, P & T Committees often received drug information passively from pharmaceutical manufacturers that was biased and of poor quality. In this era of dramatically increased drug costs, biotechnology, and information availability, the *Format* empowers health systems to proactively request specific information from manufactures that will allow them to more accurately determine the total value that a drug brings to their population as the basis for accepting or rejecting a drug for its formulary.

16. 21 C.F.R. 312.80 (2006) (referring to "life-threatening and severely debilitating illnesses"); 21 C.F.R. 314.610 (2006) (referring to ethics and feasibility).

17. See Wayne L. Pines, *A History and Perspective on Direct-to-Consumer Promotion*, 54 FOOD & DRUG L.J. 489 (1999). In hindsight, there were harbingers of direct-to-consumer advertising even in the 1960s, including the

third-party entity payors—employers, insurance companies and other managed-care organizations, and governments—were barely present in this pre-Medicare and -Medicaid era. Today, commentators who speak about drug consumers typically have patients in mind, as in “direct-to-consumer advertising,”<sup>18</sup> and patients are indeed central to the group of drug consumers.<sup>19</sup> But physicians still account for the lion’s share of prescription drug advertising and promotion budgets.<sup>20</sup> Third-party payors have also become a large sector in their own right: today the question of which prescription drug to buy can be overtly a business or a public-policy decision as well as one for a learned practitioner to make, and many entities have emerged as decision-makers.<sup>21</sup> Brought together as “consumers,” these three groups—patients, physicians, and entities—vary from the relatively unchanging, unitary publics that other regulated industries serve.

Fifth and finally, the forward-looking approach with which we began this Essay needs reexamination: regulation must include more hindsight. The more static mode of regulation in other sectors features rule-writing that

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patient packet insert, first mandated for asthma inhalers and later made more famous as an accompaniment to the sale of birth control pills. *Id.* at 490. But a common divider between present permissive conditions and the ban on direct-to-consumer marketing of the past is *Virginia State Board of Pharmacy v. Virginia Citizens Consumer Council, Inc.*, 425 U.S. 748 (1976), where the Supreme Court struck down a state law that prohibited pharmacists from advertising prescription drug prices to the public.

18. 21 C.F.R. 312.80 (2006) (referring to “life-threatening and severely debilitating illnesses”); 21 C.F.R. 314.610 (2006) (referring to ethics and feasibility).

19. See *infra* Parts I.C. & II.B. (asking “What is it like to consume this drug?”).

20. For a good pie-chart breakdown, see U.S. GEN. ACCOUNTING OFFICE, GAO REP. NO. 03-177, *PRESCRIPTION DRUGS: FDA OVERSIGHT OF DIRECT-TO-CONSUMER ADVERTISING HAS LIMITATIONS* 11 (2002).

21. For example, the chief pharmacist of General Motors announced in June 2006 that if all 250,000 persons with GM-supplied drug coverage switched from a patented cholesterol-lowering drug to a generic, the company’s “annual bill for the treatment would fall by as much as 59 percent, to \$82 million.” *GM’s Health Plans Try to Save by Going Generic Route*, CHI. TRIB., Jun. 29, 2006, § 3 (Business), at 6. On governments as drug-buying decision-makers, see Sheryl Gay Stolberg, *House Rejects Coverage of Impotence Pills*, N.Y. TIMES, Jun. 25, 2005, at A10 (reporting decision by the federal government not to allow states to use Medicaid funds to pay for erectile-dysfunction drugs for sex offenders).

mainly addresses the future. Experience matters here and there. For example, when the federal government began to issue motor-vehicle safety standards in the late 1960s, nobody foresaw the rise of feasible passive-restraint technology. After it emerged, however, rules needed revision, and today the car you drive likely contains a pair of mandatory airbags. With any prescription drug, experience matters much more, because utility to consumers can exist only in consumer experience. Accordingly, in this Essay we endorse a significant increase in post-marketing regulatory attention.

At the same time, we do not endorse an increase in the net number of rules; our ideal regulatory regime would contain fewer rules. This Essay is written in the spirit of "the new regulation" or "market-based regulation," an academic literature that has occupied other fields of law (especially environmental law and policy) but has curiously said nothing about prescription drugs.<sup>22</sup> In commending "more attention" while disdaining "more rules," we focus on *information*.

Information lies at the heart of the five differences between other types of regulation and the regulation of prescription drugs. What these five aspects—one, that regulators and regulated pursue the same goals, at least ostensibly; two, the danger of too much as too little regulatory control; three, the pursuit of two goods, safety and effectiveness, that often trade off against each other; four, multiple constituencies affected by regulation; and five, the importance of experience to guide future constraints—have in common is that successful outcomes do not emerge in a binary pattern. Trying only to suppress ills is futile where all relevant substances are poisons. For this industry, the indispensable aid to decision-making is information, not only for technical experts in government, but for buyers and sellers in the market. Information that

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22. For samples of "the new regulation," now more of a venerable fixture than an upstart (except in this prescription drugs context), see generally IAN AYRES & JOHN BRAITHWAITE, *RESPONSIVE REGULATION: TRANSCENDING THE DEREGULATION DEBATE* (1995). See also Robert W. Hahn & Roberts W. Stavins, *Incentive-Based Environmental Regulation: A New Era from an Old Idea?*, 18 *ECOLOGY L.Q.* 1, 8-10 (1991); Sidney A. Shapiro, *Outsourcing Government Regulation*, 53 *DUKE L.J.* 389 (2003); Richard B. Stewart, *A New Generation of Environmental Regulation?*, 29 *CAP. U. L. REV.* 21 (2001).

consumers—patients, physicians, and entities—can readily obtain enhances their consumption choices. Because prescription drugs are “safe and effective” only to the extent they enhance consumer utility, information helps to fulfill the statutory mandate of what drug regulation must seek.

## I. THE PURSUIT OF INFORMATION: QUESTIONS THAT REVISED REGULATION CAN HELP ANSWER

When regulators proclaim a new drug “safe and effective” following the detailed demands of a 1962 mandate, they deliver only a partial answer to an overarching preoccupation, “What is the value of this drug?” “Value” starts with information about the safety and the effectiveness of drugs. Today, consumers rightly emphasize these two aspects of performance and focus on safety. However, analysis from the consumer’s vantage point moves to another question about context: *Would an alternative treatment (or no treatment at all) provide equal or more utility?* Patients in particular add a query about the personal, semi-subjective encounter they can expect from any new pill, cream, injection, inhaler, or topical application: *What would it be like to consume this drug?* These questions, all central to the regulatory mission, would receive better answers from new rules to yield information after marketing.

### A. *How Safe Is This Drug?*

Keeping in mind the vantage point of our consumers—the patients, physicians, and entities that choose drugs—we note that drug consumers care a great deal about effectiveness, but regard the question of safety as primary.<sup>23</sup> The most basic worry about any new pharmaceutical substance is that it will prove poisonous, causing sickness rather than health. Following the premise that without regulatory assurances of safety, consumers will be poisoned, federal law has since 1938 compelled each manufacturer to satisfy that its drug is safe before

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23. At the end of this Essay we will note that of these three groups, entities (or third-party payors) privilege effectiveness the highest. *See infra* Conclusion. Yet even this group takes a keen interest in safety, and its interest in effectiveness is not absolute. *See infra* note 56.

marketing; only decades later was the Food Drug Cosmetic Act amended to demand effectiveness as well. Effectiveness is the more leisurely criterion, crucial but seldom urgent: an ineffective drug will inflict harm only when it precludes or interferes with an alternative course of action that offers more utility, and is otherwise benign. Accordingly, we postpone consideration of effectiveness, the lesser worry in this consumer-focused analysis, to the next section, which looks at effectiveness from the consumer vantage point by comparing drugs to their alternatives.<sup>24</sup>

Investigation into safety undertaken in pursuit of FDA approval begins with the introduction of a new drug into human bodies pursuant to a study that typically involves fewer than one hundred human subjects. This “phase 1” looks for side effects. Subsequent larger studies expose more subjects to the drug; this scrutiny, focused on effectiveness, also remains attentive to safety. Once they win approval, manufacturers must report serious and unexpected adverse effects promptly,<sup>25</sup> and the FDA also collects reports of “nonserious” adverse effects.<sup>26</sup> This scheme of relatively stringent pre-approval scrutiny followed by relatively lax scrutiny after marketing has begotten three recurring categories of safety trouble, discussed below, and a central question about effectiveness.

1. *Hidden Harmful Side Effects.* Consider phen-fen, the combination of weight loss drugs phentermine and fenfluramine, as an example of a drug that proved after marketing to have hidden harmful side effects that were severe enough to have stopped approval if known at the outset. In initial studies, phen-fen researchers followed a “crossover” design, placing individual subjects on and off the medication during the study. They observed weight loss while the medicine was being used and a rebound in weight during the placebo period. This crossover methodology enabled researchers to demonstrate effectiveness with relatively few subjects. This small size might explain why pulmonary complications did not emerge before approval.

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24. We mean to say that other ways to look at effectiveness that are valid or necessary in other contexts (e.g. clinical improvement, placebo comparisons) can be more distracting than helpful in this context of consumer regulation.

25. See 21 C.F.R. §§ 310.305, 314.80 (2004).

26. See 21 C.F.R. § 314.80(c)(2) (2004).

Regulators approved phen-fen on the basis of these elegant pilot studies, which proved effectiveness and did not reveal a lack of safety. Large-scale experience after approval confirmed that the combination of phen and fen succeeded at suppressing appetites. But after the drug combination entered widespread use—"off label," because its seller, Wyeth, never received approval to market the two substances as a single treatment<sup>27</sup>—clinicians learned that it not only suppressed appetites but also caused primary pulmonary hypertension in a small but measurable percentage of users.<sup>28</sup> Thousands of injured patients joined a class action that won a \$3.75 billion national settlement; others brought separate actions against Wyeth.<sup>29</sup>

Phen-fen illustrates the problem of hidden harmful side effects but does not convey enough of its magnitude. The danger here emerged relatively soon, before deaths mounted. Moreover, the phen-fen complication was so rare that even a small increase became obvious without dedicated search. Such obviousness would not be manifest if the complication were more common but no less noxious—for example, sudden death from a cardiac arrhythmia. A cluster of cases of primary pulmonary hypertension serves as a sentinel and initiates an investigation, but a heart attack in a patient with known risk factors, such as the obesity that typically accompanies weight-loss drugs like phen-fen, is a dog-bites-man story. Thus, a doctor whose

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27. Susan Kelleher, *Suddenly Sick: Rush Toward New Drugs Tramples Patients' Health*, SEATTLE TIMES, June 27, 2005, at A1. "Off-label" refers to uses of a prescription drug to achieve ends that are not indicated on its package inserts. The FDA approves each drug for a particular purpose, and requires the manufacturer to provide package inserts, or labeling, consistent with this approved usage. Physicians, however, may choose to prescribe the drug for other uses. Viagra, for example, was starting out as an angina drug when patients reported a sexual side effect. After being approved for erectile dysfunction, it showed good results for pulmonary hypertension and helping premature babies breathe. The label on thalidomide says leprosy, but this drug is used mainly to treat cancer and AIDS. See Klein & Tabarrok, *Who Certifies*, *supra* note 13, at 60.

28. Primary pulmonary hypertension is a disorder of the lung in which the pressure in the pulmonary artery rises for unknown reasons, causing right sided heart failure. See PULMONARY HYPERTENSION ASSOCIATION, PULMONARY HYPERTENSION: HELPFUL INFORMATION FOR PATIENTS AND FAMILIES (2002), available at [http://www.phassociation.org/Learn/Understanding\\_PH\\_broc.pdf](http://www.phassociation.org/Learn/Understanding_PH_broc.pdf).

29. Mary P. Gallagher, *Court Allows Threshold Challenge to Medical Basis of Phen-Fen Opt-Outs*, N.J. L.J., Apr. 19, 2004.

patients had slightly more heart attacks would not even notice it. She would likely attribute the increase to chance or a factor other than prescription medication. Drug-induced harm can accrete for years without provoking the concern that phen-fen quickly presented.

2. *Subtle but Real Increases in Common Problems.* In a clinical trial, researchers report adverse effects as a listing of these effects observed, the rate of their appearance among those taking the drug, and the rate found among those taking an inert compound, or placebo.<sup>30</sup> The placebo contrast is crucial because certain reported adverse effects are more difficult to interpret, especially those that are ubiquitous. Almost everyone will claim a headache now and then; how can one tell whether to blame drugs? The clinical question is not whether adverse effects are found in the study group, but whether their rate of appearance is meaningfully different than that of the placebo group.<sup>31</sup> This question in turn requires detailed statistical analysis.<sup>32</sup>

The larger the sample group, the more representative an observed parameter is likely to be: statisticians speak of "the law of large numbers."<sup>33</sup> Because a study population is only a small subset of the population of ultimate users, the study may lack statistical power to discern differences in

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30. The Code of Federal Regulations regards these protocols as central to an "adequate and well-controlled study." See 31 C.F.R. § 321.126 (2004).

31. See *Woodcock Interview*, *supra* note 14 (explaining this precept as followed at the FDA Center for Drug Evaluation and Research).

32. If an adverse effect is found in 6% of a study group and in 3% of a placebo group, one still may not be sure that the drug increases the rate of the effect. Clearly, 6% is more than 3%—double, obviously. But 6% (and 3%) are not the true rates—what would be found if one studied the drug in everybody whoever will take it—but rather the *observed* rate in a population sample. The true rate, namely what would be found among all users, not just of those in the study group, may be different. Statistical tests can tell whether the observed rate is a valid representative and thus whether a difference is genuine or rather an artifact of random variation.

33. See generally Stan Lipovetsky, *Probability, Statistics, and Stochastic Processes*, 48 *TECHNOMETRICS* 150 (2006) (book review) (placing "the law of large numbers" in its context within a statistics reference work). Consistent with the law of large numbers, a baseball player needs 502 plate appearances to qualify for a seasonal batting title. Four hits in ten at-bats yields a batting average of .400, but a player who attains that record over a season is hardly a ".400 hitter" in the league of, say, Ted Williams.

the rates of common adverse effects. The “power analysis” that biostatisticians undertake at the outset of a study to determine the minimum number of subjects is typically focused on the therapeutic effect and will obscure small differences in levels of common side effects.<sup>34</sup> Thus, subtle but real increases in the risk of common effects—those seen in the baseline normal population—may be discarded as not statistically significant. The truth might emerge only from large-number post-marketing data.

Suppose five out of one hundred people taking a placebo reported headaches, while ten out of another hundred taking a real medicine reported them. Researchers would have to confront two possibilities before drawing conclusions: first, that the rate of headaches among the real-medicine takers was genuinely higher (if perhaps not literally double); and second, that the additional five cases amounted to statistical noise. A study of a thousand subjects might be needed to discern a true difference; the truth might emerge only from large-number, post-marketing data. A real-world illustration of this problem comes from Vioxx, the popular painkiller that arthritis patients lost following findings that it more than doubled the risk of heart attack and stroke.<sup>35</sup> Until enough study subjects took Vioxx, researchers could not attribute the increase in cardiovascular complications to the drug.

3. *Harmful-Effect Information Not Adequately Shared.* For this category of danger, the June 2005 withdrawal of the drug Propulsid, used to treat excess gastric acid, provides an illustration. Propulsid, a substance approved as safe, proved deadly in use; it interfered with the heart’s electrical system, strongly enough to induce heart

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34. A power analysis seeks the minimum number of subjects to establish effectiveness: because studies are expensive, researchers seek to use as few human beings as will yield valid conclusions. See Power and Precision, *What is Power Analysis?*, [http://www.power-analysis.com/power\\_analysis.htm](http://www.power-analysis.com/power_analysis.htm) (providing an overview of power analysis as determined by proprietary software). While serving as chief counsel to the FDA in the 1970s, drug-law scholar Richard Merrill identified the problem of too-small samples as a barrier to meaningful safety research. Richard A. Merrill, *Risk-Benefit Decisionmaking by the Food and Drug Administration*, 45 GEO. WASH. L. REV. 994, 1005 n.59 (1977).

35. *Drug Industry Weathers Horrid Year and Outlook Appears Rocky*, FOOD & DRUG L. WKLY., Business Update, Jan. 14, 2005.

arrhythmia and death.<sup>36</sup> For years, officials knew the drug was dangerous. Its manufacturer, Johnson & Johnson, had been hearing from the FDA about the dangers of the drug beginning in January 1995, when officials “told Johnson & Johnson that the drug was causing life-threatening arrhythmias.”<sup>37</sup> The agency expressed its concerns privately to the manufacturer over the course of a decade. During this time, Johnson & Johnson continued to market Propulsid at great profit; harmful side effects continued even after the company paid \$90 million in 2004 to settle claims alleging that Propulsid was responsible for three hundred deaths and sixteen thousand nonfatal injuries.<sup>38</sup> Like the other two recurring safety problems just mentioned, harmful-effects data is a problem of missing information.

*B. Would an Alternative Treatment (or No Treatment at All) Provide Equal or More Utility?*

One prominent physician-pharmacologist, Jerry Avorn, has said he would like to see “the following revenue-crippling government evaluation” on most new drugs: “This new medication has not been shown to be any better than currently available products, and has a much more limited safety record. There is no evidence that its higher price is accompanied by any demonstrated therapeutic advantage.”<sup>39</sup>

Avorn wrote in a wry spirit rather than to propose regulatory reform, but his suggestion would offer benefit to consumers. If the content of this hypothetical evaluation happens to be true about a particular drug, safety-and-effectiveness (or their sum, utility) becomes stronger after consumers gain access to this truth: many would avoid the drug in favor of a better alternative. For the minority of consumers who would do well with this new alternative, information again becomes the key to utility. In the post-

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36. See Gardiner Harris & Eric Koli, *Lucrative Drug, Danger Signals and the F.D.A.*, N.Y. TIMES, June 10, 2005, at A1.

37. *Id.* at C6.

38. *Id.*

39. AVORN, *supra* note 10, at 365. Avorn has called this suggestion wishful thinking. *Id.*

1962 world, where most high-revenue drugs are members of categories and cost-containment pressures have grown strong, it is now impossible to think of utility without comparing each drug to other treatments, and to no treatment at all.<sup>40</sup>

Many contemporary observers of the pharmaceutical industry would like to see regulators address how each drug compares to alternatives.<sup>41</sup> They keep alive a stance that the congressional Office of Technology Assessment, now defunct,<sup>42</sup> brought to official federal attention in 1994 with its report that found an urgent need to study prescription drugs in comparative perspective.<sup>43</sup> The FDA has not embraced this drive. While regarding *How safe is this drug?* and *How effective is this drug?* as questions at the center of its mandate, until recently the agency has been leery of regulating comparative effectiveness—or what regulators and observers more commonly (especially when taking the position that the subject is out of regulatory bounds) call “comparative efficacy” or “relative efficacy.”<sup>44</sup>

Avoiding comparative effectiveness seems at first blush to have support in the 1962 amendments that introduced effectiveness to the Food Drug Cosmetic Act. The

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40. See *Format for Formulary Submissions*, *supra* note 15 (offering to formulary writers an understanding of how to judge the value a new drug).

41. See ANGELL, *supra* note 10 (arguing that no reform idea is more important). See also Robert Pear, *Congress Weighs Drug Comparison*, N.Y. TIMES, Aug. 24, 2003, at 18 (“How does Lipitor stack up against Zocor for lowering cholesterol? How does Prilosec compare with Protonix for ulcers and heartburn? How do the long-term effects of Vioxx and Celebrex compare with those of older drugs for arthritis, like Motrin and Naprosyn?”).

42. On its decline and fall, see PHILIP J. HILTS, PROTECTING AMERICA'S HEALTH: THE FDA, BUSINESS, AND ONE HUNDRED YEARS OF REGULATION 212-13 (2003); Anita Bernstein, *Engendered by Technologies*, 80 N.C. L. REV. 1, 107 (2001).

43. See David Brown, *Patient Databases Don't Show Which Treatment Works Best, Study Finds*, WASH. POST, Oct. 25, 1994, at A8. The Office of Technology Assessment also explored the question of why such studies are so seldom done. One major impediment is lack of prestige: funders like to pay for small studies of new treatments, not large, unglamorous tracking of longstanding ones. *Id.*

44. The most accurate term would be “comparative efficacy”—that is, an assessment of clinical improvement. Because this term and “relative efficacy” are uncommon in the drug policy literature, we go along with the prevalent “comparative effectiveness.”

amendment's chief sponsor, Senator Estes Kefauver, contributed a morsel of legislative history that some have interpreted as an obstacle to comparison. "I want to make clear," Kefauver declared in 1961, that "it was only intended that the manufacturer satisfy the Food and Drug Administration that it [a drug] was efficacious for the use intended and claimed by the manufacturer, not trying to say it is better than some other drug or poorer than some other drug."<sup>45</sup>

Although this sentence perhaps did not "make clear" very much, one commentator offers a succinct translation: "Congress did not intend for sponsors to prove a new drug has greater relative efficacy than its competitors" in order to win approval.<sup>46</sup> Under this plausible construction, regulators may seek to extract and disseminate information about drug comparisons;<sup>47</sup> the only constraint that Kefauver's remark imposes is these regulators may not withhold approval of a safe and effective drug merely because the drug does not outperform competitors in its class. Senator Kefauver was speaking about yes/no decisions; his statement does not keep comparative-effectiveness review out of the statutory mandate.<sup>48</sup> Further support for this conclusion comes from an effort that Speaker of the House of Representatives Newt Gingrich led in the mid-1990s: Gingrich sponsored draft legislation that

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45. *Hearings Before the Subcomm. on Antitrust and Monopoly of the S. Comm. on the Judiciary*, 87th Cong. 417 (1961). Jerry Avorn has expressed his belief that the FDA has limited powers with respect to regulating comparative efficacy. See AVORN, *supra* note 10, at 380-81; Telephone Interview with Jerry Avorn, Professor of Medicine, Harvard Medical School, and Chief of the Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital (Feb. 11, 2004).

46. Kulynych, *supra* note 3, at 133.

47. It may not be necessary to parse the Kefauver remark: comments that members of Congress make about a statute probably do not constrain the actions of an agency. See Thomas W. Merrill, *Textualism and the Future of the Chevron Doctrine*, 72 WASH. U. L.Q. 351, 365 (1994) (discussing this understanding, and noting that forceful advocacy from Justice Scalia has made it stronger).

48. See generally *Joint Hearing of the International Trade Subcomm. and the Health Care Subcomm. of the S. Finance Comm.*, 108th Cong. (2004) (presenting testimony from FDA representative William K. Hubbard that while cost-effectiveness determinations may lie outside the FDA mandate, comparative efficacy falls inside it, especially if the FDA would not undertake to remove or ban a drug that does not outperform its competitors).

would have forbidden “drug reviewers to compare the effectiveness of two commercial drugs with one another in determining whether to approve a new one.”<sup>49</sup> The defeat of this effort indicates that the FDA had then, and still has, authority to promote comparative effectiveness.<sup>50</sup> The best way to promote comparative effectiveness is through information.

As with *How safe and effective is this drug?*, insight into our question of comparisons to alternatives emerges from contemporary experience. The plummeting of costly COX-2 inhibitors—Vioxx and Bextra withdrawn, Celebrex alive but shrouded in gloomy warnings—brought glory onto the humbler non-steroidal anti-inflammatory trinity: aspirin, ibuprofen, and naproxen.<sup>51</sup> One study comparing nabumetone, a name-brand non-steroidal anti-inflammatory agent, with ibuprofen found a big gap in pharmacy wholesale costs: a month’s supply of the nabumetone cost \$58.68, compared to \$8.64 for ibuprofen.<sup>52</sup>

A more notorious contemporary story about alternatives features Synthroid, the brand-name version of levothyroxine. When researchers at the University of California at San Francisco concluded a study in 1990 finding this name-brand hormone no better than three generics, the manufacturer of Synthroid, which had paid for the study, responded first by discrediting the early findings and then by pressuring the researchers to withdraw their paper from the *Journal of the American Medical Association*, where it had been scheduled for publication in

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49. HILTS, *supra* note 42, at 319. This sentence appears to use effectiveness as roughly synonymous with efficacy.

50. See *id.* at 325-33 (describing the coalition politics that ended Gingrich’s plans to hobble the FDA).

51. See *FDA Doctor Questions Need for Any Drugs from the COX-2 Class*, BIO WORLD TODAY, Feb. 18, 2005.

52. Cited in Larry D. Sasich & Sidney M. Wolfe, *HRG Comments on Direct-to-Consumer Prescription Drug Promotion*, PUBLIC CITIZEN (August 12, 1996), available at <http://www.citizen.org/publications/release.cfm?ID=6596>. The prices were for minimum recommended doses. *Id.* Physician Sidney Wolfe and pharmacist Larry Sasich responded to these findings by issuing a general prescription for more information. “It is difficult to imagine a set of circumstances in which a prescription drug consumer given accurate complete comparative information would accept the unknown risk of toxicity and the higher cost of nabumetone as a treatment over ibuprofen or naproxen.” *Id.*

1995. Their findings of bioequivalence—that Synthroid accomplishes nothing that its generic competitors cannot do—were not published until 1997, costing the public an estimated \$800 million in the Synthroid premium, or money for nothing, over the two years of suppression.<sup>53</sup> Other comparative studies could tell consumers more about the utility of alternative treatments.

### C. *What Is It Like to Consume This Drug?*

Next to the lofty mandate of “safe and effective,” this final question may seem a little shallow. Amateurs answer it with reference to their feelings, not the professional expertise for which the FDA achieved fame and high public approval. “Safe” and “effective,” both gradable rather than absolute adjectives,<sup>54</sup> were never so pure as a dismisser of this question might presume, however, and when regulatory policy balances these against each other in making determinations about approval,<sup>55</sup> it shows that even these domains of science contain space for flexibility.

Direct-to-consumer advertising of our well-worn example, Vioxx, shows how closely semi-subjective experiences fit inside the traditional domain of regulation. In 2002, three years before the drug was withdrawn, the FDA gave Merck permission to advertise Vioxx as “gentler

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53. See Drummond Rennie, *Thyroid Storm*, 277 J. AM. MED. ASSOC. 1238 (1997).

54. See *supra* notes 8-9 and accompanying text.

55. See *supra* notes 14-16 and accompanying text. One prominent drug-law scholar has written that regulators engaged in this balance even before the 1962 amendments that introduced effectiveness as a criterion for approval:

Although FDA's authority [in 1938-1962] over concededly 'new' drugs was formally limited to confirming their safety, agency reviewers often felt obliged to consider their therapeutic effectiveness as well. Drugs were, after all, biologically active agents and thus inherently posed some risk. Whether a particular drug could be considered 'safe,' therefore, depended on whether it offered medical benefits that outweighed the risk. Increasingly, FDA found itself engaged in an informal form of risk-benefit assessment for new drugs prior to marketing.

Richard A. Merrill, *The Architecture of Government Regulation of Medical Products*, 82 VA. L. REV. 1753, 1764 (1996) (citation omitted).

to the stomach.”<sup>56</sup> This soundbite recites in simple English the observed phenomenon that Vioxx and other COX-2 inhibitors have a relatively low association with endoscopically demonstrable gastric ulceration. But patients might have wanted to know that COX-2 inhibitors were never shown to have produced a more pleasant subjective experience with regard to gastrointestinal symptoms<sup>57</sup>—a gloss on “gentler to the stomach” that lay persons might well have put on Merck’s claim. More information in response to *What is it like to consume this drug?* would have clarified the topic that a manufacturer broached, with FDA approval, but did not resolve.

The question of *What is it like to consume this drug?* is a crucial component of the safety-and-effectiveness regulatory mission. The subjective experience of consumption affects whether patients will follow a drug regimen, thus playing a role in effectiveness. It is impossible to study the clinical impact of any treatment for a chronic condition without studying compliance.<sup>58</sup> Compliance issues are at the heart of, among other treated conditions, current (pre-vaccine) HIV therapy, which can require patients to take many pills each day under strenuous and varying circumstances. Keeping track of patients’ subjective responses to medication is so central to studying effectiveness that researchers use a patented device called the “medication event monitoring system” to chart compliance by recording the date and time that a pill container is opened.

Noncompliant patients are not the only constituency that has something pertinent to say about the subjective experience of taking a drug. Anecdotes about futility can round out the safety-and-effectiveness picture with details that otherwise might fail to draw the attention of formulary-writers and other repeat-player choosers of

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56. National Briefs, HOUS. CHRON., Apr. 12, 2002, at A21.

57. See NORTIN M. HADLER, OCCUPATIONAL MUSCULOSKELETAL DISORDERS 74 (3d ed. 2005).

58. The problem has concerned public health researchers for many years. See Jim Shamp, *Prescription Dereliction*, HERALD-SUN, May 20, 2001, at G2 (noting that a 1979 study “identified more than 200 variables that interfered with compliance.”).

which drugs to buy.<sup>59</sup> Managed-care organizations do have incentives to care about safety and effectiveness, but so did the physician circa 1962 (reputation, professional pride, bonds with patients), and today this physician perspective in isolation is regarded as inadequate to monitor these criteria without more input.<sup>60</sup> Moreover, many clinical aspects of drug quality do not reach the attention of decision-making personnel who work for managed-care organizations.<sup>61</sup> When patients answer our question with something like, "Terrible, it stinks," then, public-health consequences follow.

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59. Three years ago, Paul Fanning, a friend and co-author of one of us (Anita), was receiving chemotherapy for his lung cancer. When the treatment made him severely nauseated, his insurer supplied him with an anti-nausea prescription drug. Paul agreed to more chemotherapy knowing his nausea could be controlled, but after the second round began, he learned that the insurer had withdrawn coverage of the effective drug. He received an ineffective drug instead, and the insurer ignored his protests about ineffectiveness. Paul refused further chemotherapy and all other treatments, and died about five months later. He hated to complain; we would not have known of his experience had Anita not mentioned this project-in-progress. Paul told the story after she relayed to him the contention that managed-cared organizations have sufficient incentives to enforce effectiveness. See, e.g., Note, *FDA Reform and the European Medicines Evaluation Agency*, 108 HARV. L. REV. 2009, 2019-23 (1995) (arguing that the FDA should regard EMEA approval as sufficient to satisfy the statutory requirement of "substantial evidence" of drug effectiveness); Henry I. Miller, *Vaccine Development a Casualty of Flawed Public Policy*, HOOVER INST. WKLY. ESSAYS, May 5, 2003, available at <http://www.hoover.org/pubaffairs/dailyreport/archive/2848681.html> (making a similar argument for vaccine approval). Paul pointed out that if his drug had promised to cure him of cancer, or put him back to work paying premiums, then the managed-care organization would indeed have cared to monitor its performance. For palliative treatment of the terminally ill, however—and for other therapies—effectiveness will not appear on a managed-care balance sheet.

60. See Barbara Marticelli McGarey, Comment, *Pharmaceutical Manufacturers and Consumer-Directed Information—Enhancing the Safety of Prescription Drug Use*, 34 CATH. U. L. REV. 117, 122 (1984) (arguing that "if prescription drugs are to be used safely and effectively, the consumer must be able to assist the prescribing physician in weighing the risks and benefits of drug therapy, and in monitoring that course of therapy.").

61. Reports of unsafety and ineffectiveness have to travel some distance from affected patients, through a chain of individuals. For instance, imagine a patient harmed or not helped by a particular drug. She might be married to an insured employee. The patient might convey her story to her husband the employee—or she might not. The husband might talk to a human-resources manager—or he might not. The manager might talk to his supervisor. The administrator in charge of insurance contracts might make a decision—if she felt motivated to overcome inertia.

Understanding what it is like to take a drug would benefit all three of the “new consumers” highlighted in this Essay. Patients’ bodies are on the line. Prescribing physicians who must choose among treatments would want data relating to the complaints, compliance, abandonment, and adaptations that patients express and reveal after they start new drug regimens. Formulary writers could take user satisfaction into account in choosing which drugs to buy. Third-party payors would make better actuarial projections about responses to drugs when they know how patients perceive these treatments. Even manufacturers would gain from what would be in effect disinterested and well-designed supplementary market research about the products they and their competitors sell.

Like comparative effectiveness, the study of lay perceptions of drugs once lay outside what the FDA saw as its ambit, and more recently has come closer to its agenda. In 2004, a former associate commissioner of external relations at the FDA challenged the agency’s Division of Drug Marketing, Advertising, and Communications to make determinations about the promotional material it reviews—for “fair balance,” “adequate provision,” and the like—using social science rather than coming to ad hoc, unsubstantiated conclusions.<sup>62</sup> The “FDA had been planning to improve social science at the agency for at least a year,” its newsletter reported, somewhat sheepishly, in a December 2004 announcement about the agency’s plans to study how lay consumers perceive health claims about foods and dietary supplements.<sup>63</sup> Just as perceptions of promotional material are part of the “fair balance” mix, patient experiences with drugs belong within judgments of their safety and effectiveness. Gathering answers to the question of “What is it like to consume this drug?” fits within the FDA’s informal motto of “science rules,”<sup>64</sup> not only because subjective experiences affect results, but because these data can be reliably measured.

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62. Peter Pitts, *Put More Science in Social Science*, PHARMACEUTICAL EXECUTIVE, Sept. 1, 2004, at 186.

63. *FDA Plans to Study Consumer Responses to Health Claims*, FDA WEEK, Dec. 17, 2004. With a touch of interagency rivalry, the announcement mentioned that the FDA sought “solid approaches for measuring consumer perception like the science that the Federal Trade Commission uses.”

64. Pitts, *supra* note 62.

## II. THE PRODUCTION OF INFORMATION: ANSWERS

Here we link “the information prescription” with answers to the questions that consumers ask before choosing whether to buy products in this market.

### A. “How Safe and Effective Is This Drug?": Answers

We endorse three recommendations—first, “pharmacovigilance;” second, the public registration of drug trials; and third, improved definitions of statutory terms—that appear in the literature as solutions to a range of policy problems. Here we note the centrality of information to all three, and examine them in terms of what they reveal to consumers and regulators.

1. *Codifying Pharmacovigilance.* “Pharmacovigilance,” a venerable concern about adverse responses to treatment,<sup>65</sup> may be extended to describe the ongoing investigation into prescription drugs in use that ought to follow regulatory approval. Two academic physicians elaborated on this concept following the saga of Vioxx, launched in 1999 as a treatment for arthritis and a star drug until findings emerged linking it to heart attacks and other vascular complications.<sup>66</sup> Merck withdrew Vioxx from the market in September 2004. Unprompted by either regulation or personal-injury litigation, Merck had found the risks on its own, in a study called APPROVe.

“Merck has always believed that prospective, randomized, controlled clinical trials are the best way to evaluate the safety of medicines,” said Peter S. Kim, Ph.D., the president of Merck Research Laboratories, in a much-reported quote. “APPROVe is precisely this type of study—and it has provided us with new data on the cardiovascular profile of VIOXX.”<sup>67</sup> What Dr. Kim did not add was that Merck did not sponsor the study to monitor the safety of its

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65. See generally Philip Routledge, *150 Years of Pharmacovigilance*, 351 LANCET 1200 (1998) (reporting the formation of a commission to monitor anesthesia-related deaths following an adverse incident in 1848).

66. See Simon R.J. Maxwell & David J. Webb, *COX-2 Selective Inhibitors—Important Lessons Learned*, 365 LANCET 449, 450 (2005).

67. Quoted in *Merck Withdraws Vioxx Based on 3-Year Data from APPROVe Clinical Trial*, SCI. LETTER, Oct. 26, 2004 [hereinafter *Merck Withdraws*].

extremely successful product.<sup>68</sup> The name APPROVe did not refer to ongoing duties to retain FDA approval but to “adenomatous polyp prevention on Vioxx”: Merck hoped to determine that Vioxx prevented the recurrence of colorectal polyps in patients with a history of colorectal adenomas.<sup>69</sup> Absent this motive to expand business, Merck would have left well enough alone, and foregone the study that proved to be the undoing of its bestseller.<sup>70</sup>

The APPROVe study provides an unintentionally aptly named illustration of the pharmacovigilance that ought to ensue after approval. That Vioxx causes significant cardiovascular risks was not shocking, in hindsight. Vioxx is a COX-2 inhibitor. Prostacyclin inhibits platelet aggregation and vasoconstriction; COX-2 inhibitors decrease prostacyclin. Therefore Vioxx, as a COX-2 inhibitor, could elevate blood pressure and promote thrombosis. Years before the dangers of Vioxx came to light, studies had noted this COX-2 inhibitor risk.<sup>71</sup>

This mechanistic assessment did not necessarily make any COX-2 inhibitor a bad drug, *ex ante*. Clinical experience could yield a contrary result.<sup>72</sup> But, in hindsight, it shows the need for regulators to mandate pharmacovigilance as a condition for continued approval. Under a pharmacovigilance model, approval ceases to be a static phenomenon, and undergoes continuous reexamination. Manufacturers have a duty to seek and report additional data where articulable standards declare that it is needed.

A pharmacovigilance rule in the Code of Federal Regulations could begin as follows: “Where the safety studies on which a drug’s approval is based are suggestive

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68. Sales were \$2.5 billion in 2003, the drug’s last full year of life on the market. Julie Schmit & Kevin McCoy, *FDA Panel Supports Return of Vioxx*, USA TODAY, Feb. 21, 2005, at B1.

69. *Merck Withdraws*, *supra* note 67.

70. Merck lost \$25 billion in market capitalization following its withdrawal announcement, and then lost another \$15 billion before its stock price hit bottom in November 2004. Steven Milloy, *Merck’s Costly Withdrawal*, N.Y. SUN, Feb. 24, 2005, available at [http://www.csrwatch.com/merck\\_withdrawal.htm](http://www.csrwatch.com/merck_withdrawal.htm).

71. G.A. FitzGerald et al., *COX-2 Inhibitors and the Cardiovascular System*, 19 (Suppl. 25) CLINICAL & EXPERIMENTAL RHEUMATOLOGY S-31, S-31 (2001).

72. Consider the inverse: every promising cancer therapy began with an appealing mechanistic argument; and yet cancer is still with us.

of clinically significant adverse alternative results, the FDA may mandate additional post-marketing studies as a condition of approval." Statistical techniques aid the inquiry.<sup>73</sup> The principle of pharmacovigilance identifies opportunities to infer the possibility of danger; regulations should provide expressly for pharmacovigilance-based requirements of more study.

The Code contains a model for this rule: food additives of questionable safety can receive provisional approval, attached to conditions that mandate the withdrawal of approval when a manufacturer fails to maintain vigilant safety research or to report what its ongoing studies say.<sup>74</sup> Consistent with the utility theme that pervades this Essay, the rule could elaborate that these post-marketing studies should be ordered with attention to the costs of being wrong, taking into account the likely effectiveness of the drug. Also borrowing from existing regulation, the pharmacovigilance rule could provide in its concluding sentence that "these postmarketing studies shall be

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73. For example, a low incidence level of adverse effects would suggest that a drug is safe; a high incidence level suggests it is dangerous. But because chance rather than an agent can cause the adverse effect, the statistical convention of  $p = 0.5$  provides that when the probability about being wrong on causation is less than five percent, the scientific community will accept a linkage as statistically significant. Biostatisticians at the FDA use more advanced techniques than this "p value" convention, but they too have to deal with findings of exposure coupled with adverse effects that raise questions about causation. For a particular drug,  $p = 0.06$  might not be not high enough to say dangerous, but it is also too high to ignore.

74. [W]hen new information raises a substantial question about the safety or functionality of the substance but there is a reasonable certainty that the substance is not harmful and that no harm to the public health will result from the continued use of the substance for a limited period of time while the question raised is being resolved by further study,

21 C.F.R. § 180.1 (2004), the Code provides that the FDA can issue a limited approval of this food additive, conditioned on further study and twice-annual reports by the manufacturer:

If the progress report is inadequate or if the Commissioner concludes that the studies are not being pursued promptly and diligently or if interim results indicate a reasonable likelihood that a health hazard exists, an order will promptly be published in the Federal Register revoking the interim food additive regulation effective upon publication.

*Id.*

reported annually until FDA notifies the applicant, in writing, that the agency concurs with the applicant's determination that the study commitment has been fulfilled or that the study is either no longer feasible or would no longer provide useful information."<sup>75</sup>

So understood, pharmacovigilance extends current regulations, which now dichotomize too sharply between pre- and post-approval surveillance. The present Part 314 of Title 21 of the Code of Federal Regulations, called "Applications," is divided into thirteen subsections, of which only two now address post-approval duties. In contrast to the stringent demands before approval, the FDA post-approval limits manufacturers' duties mainly to the reporting of adverse incidence and collection of relatively minor miscellaneous danger.<sup>76</sup> Only for exceptional categories—accelerated approval or pediatric applications—do the regulations provide for FDA-mandated "postmarketing study commitments."<sup>77</sup> Pharmacovigilance would increase these commitments.

Findings on effectiveness as well as safety can emerge from pharmacovigilance. Physicians Thomas G. Roberts, Jr. and Bruce A. Chabner have proposed a new rule that uses the tradeoff approach described above.<sup>78</sup> Roberts and Chabner would extend "fast track" drug approval to encourage improvement in certain types of drugs, especially anticancer agents.<sup>79</sup> They endorse new rules to authorize preliminary approval if a drug achieved encouraging results in early efficacy trials, but only if at the time of its new-drug application it had "initiated studies to identify subgroups of patients who are likely to have responses."<sup>80</sup> Present regulatory conditions, Roberts and Chabner explain, give manufacturers no incentive to continue their

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75. *Id.*

76. 21 C.F.R. §§ 314.80, 314.81 (2004).

77. 21 C.F.R. § 314.81(b)(2)(vii) (2004).

78. See Thomas G. Roberts, Jr. & Bruce A. Chabner, *Beyond Fast Track for Drug Approvals*, 351 NEW ENG. J. MED. 501, 501-02 (2004).

79. "Fast track" refers to the FDA's obligation to rush new drugs to market when they fulfill an "unmet medical need." Food and Drug Modernization Act of 1997, Pub. L. No. 105-115, § 112(a)(1), 111 Stat. 2296, 2309, 21 U.S.C. § 356(a) (1) (2000).

80. Roberts & Chabner, *supra* note 78, at 504.

research to determine which classes of patients are likely to benefit from their drug once it has been approved. They suggest “that the FDA require that a minimal percentage of drug sales,” perhaps five percent, “be allocated either to studies focused on identifying subgroups of patients who are likely to have responses or to the NIH for its sponsorship of related research.”<sup>81</sup> Patients who take cancer drugs would find regulatory innovation of this kind especially welcome, as these drugs have an exceptionally weak track record.<sup>82</sup> Another field of post-marketing study that manufacturers could undertake is what off-label clinical experience with their drugs teaches—an enormous base of potential information, now gathered fitfully and in the form of anecdotes.<sup>83</sup>

Pharmacovigilance, as Roberts and Chabner present it, reminds policymakers that just as the conclusion of “safe” cannot be static, so too must judgments of effectiveness be forced to stand up over time. Initial studies that show effectiveness to the satisfaction of regulators become the basis of approvals—and then subsequent studies often refute or question these older findings of effects. One review returned to all original clinical studies published in three major medical journals between 1990 and 2003 that were cited more than one thousand times to see how their conclusions fared later.<sup>84</sup> The reviewer, physician-epidemiologist John Ioannidis, found that forty-five out of forty-nine highly cited studies had reported that a particular intervention was effective. Subsequent research contradicted seven of these findings of effectiveness, Ioannidis reported; for another seven, these follow-ups found

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81. *Id.*

82. Cf. Merrill Goozner, *Prescription for Reform*, WASH. POST, Dec. 1, 2003, at A23.

83. See Mitchell Oates, Note, *Facilitating Informed Medical Treatment Through Production and Disclosure of Research into Off-Label Uses of Pharmaceuticals*, 80 N.Y.U. L. REV. 1272 (2005). The author proposes that drug manufacturers be compensated for doing this research and sharing it with the public, but admits to some difficulty in identifying a suitable means of compensation. *Id.* at 1305-06 (noting that the traditional way to reward pharmaceutical companies, “market exclusivity,” is extremely costly to the public). On the valuable information generated by off-label experimentation, see Klein & Tabarrok, *Who Certifies*, *supra* note 13.

84. John P. A. Ioannidis, *Contradicted and Initially Stronger Effects in Highly Cited Research*, 294 JAMA 218 (2005).

that the intervention had a significantly weaker effect than what the early study had announced.<sup>85</sup>

To some critics, demand for more tests may seem like yet another costly, innovation-stifling regulatory burden. The example of Vioxx may again be instructive. Merck undertook the study that ultimately showed an increased rate of cardiovascular events—its APPROVe trial—to broaden the market for Vioxx by seeking evidence to support a claim that the drug prevented familial adenomatous polyposis, or FAP. Casual observation of the rough size of this potential secondary market helps to estimate the magnitude of additional studies as a new regulatory onus. While a manufacturer might prefer to account for costs associated with the original studies as costs of the post-marketing studies, a fairer method is to consider only the marginal costs. These costs can be inferred by studying the marginal increases to the market; we assume that Merck would not invest  $x+y$  to augment sales revenues by  $x$ . FAP is an extremely rare condition, affecting approximately 10,000 people in the United States.<sup>86</sup> Perhaps Merck had high hopes beyond FAP. It might have pursued this indication to gain insights into the basic biology of polyp formation to help develop other products. But this payoff would come long in the future, if at all. Rule-writers may infer that this manufacturer did not find the cost of its study—a model for the pharmacovigilance we recommend—ruinous or excessive.<sup>87</sup>

Consider Vioxx again by way of summarizing what pharmacovigilance has to offer. A review panel might have

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85. *Id.* at 220.

86. Stanford Comprehensive Cancer Center, Familial Adenomatous Polyposis, <http://cancer.stanford.edu/gastrocolo/familial.html> (last visited Sept. 5, 2005).

87. Outside experts could join the pharmacovigilance project at relatively little cost, should the FDA lack the capacity for complete review of all proposed drugs. Another administrative unit within Health and Human Services, the Center for Scientific Review, could comment on the possibility of adverse alternative results and direct particular study. The Center now uses more than 11,000 independent scientists to review proposals for the National Institutes of Health, and could easily extend its expertise to consultation about pharmacovigilance at the time of application. See *generally* Center for Scientific Review, Welcome to CSR, Jan. 21, 2006, <http://cms.csr.nih.gov/AboutCSR/Welcome+to+CSR> (last visited Sept. 2, 2006) (noting that the Center conducts most of its reviews for the NIH, but supports other federal agencies as well).

noted the issue of prostacyclin inhibition as a concern about Vioxx and recommended a study. Depending on the severity of the risk as researchers would quantify it—that is, of the likelihood of it being clinically validated, as well as its consequences—the FDA could insist on postmarketing studies on which continued approval would be contingent. Review panels would work best relatively sheltered from media and political scrutiny, and would preferably be smaller than the FDA's current "problem review" panels.<sup>88</sup> The next Vioxx awaits this regulatory interception.

*2. Old Wine in a New Bottle: Public Registration of Drug Trials.* Reformers have long called for drug trials to be made public before sponsors know what the studies will say.<sup>89</sup> At present, pharmaceutical companies that sponsor clinical trials are free to release selectively only a portion of what they learn, unless the treatments they study involve life-threatening conditions.<sup>90</sup> About half of the one million clinical trials that took place in the last fifty years yielded no study results to the public.<sup>91</sup> Frustrated by what they called the challenge of trying to "evaluate what's not there," editors of twelve prominent medical journals united in 2004 around a new stance: they would not publish the outcomes of clinical trials unless the trials had been registered in advance in a public database.<sup>92</sup>

One notorious illustration of the problem involves the antidepressant Paxil and manufacturer, GlaxoSmithKline. When a GlaxoSmithKline-funded study found Paxil to be effective for adolescent depression, the company permitted researchers to publish these findings in the *American*

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88. One Vioxx panel had more than thirty members. *Merck's Vioxx May Be Sold Again, FDA Advisors Rule (Update 2)*, BLOOMBERG.COM (Feb. 18, 2005), [http://www.bloomberg.com/apps/news?pid=10000087&sid=aM29b\\_4WufM8](http://www.bloomberg.com/apps/news?pid=10000087&sid=aM29b_4WufM8) (last visited Feb. 23, 2006).

89. *See Should There Be Mandatory Registration of Drug and Device Trials to Lessen Selective Reporting of Results?*, 19 THE BACK LETTER 112, 112 (2004) [hereinafter *Mandatory Registration*] (noting that this suggestion is more than thirty years old).

90. Rita Rubin, *Drugmakers to Voluntarily Post Info Online About Clinical Trials*, USA TODAY, Jan. 7, 2005, at B7.

91. *See Mandatory Registration*, *supra* note 89, at 112.

92. Editorial, *Register All Clinical Drug Trials*, HARTFORD COURANT, Oct. 4, 2004, at A8.

*Academy of Child and Adolescent Psychiatry*. When another GlaxoSmithKline-sponsored trial raised concerns about children having suicidal thoughts while on Paxil, however, the company kept this finding from the public, declining to submit it for publication.<sup>93</sup> Questions about the legality of this suppression remain unresolved because GlaxoSmithKline settled a fraud action brought by New York Attorney General Eliot Spitzer, paying \$2.5 million and agreeing to publish data on all “relevant studies” of Paxil.<sup>94</sup> Embarrassed by the prosecution and tacit admission of wrongdoing by one of its largest members, the Pharmaceuticals Research and Manufacturers of America, the industry trade organization, announced in early 2005 that member-manufacturers would soon start complying with a voluntary mandate to post information about their ongoing clinical trials.<sup>95</sup>

This concession fell short of a new federal law that would compel manufacturers to register all their “significant clinical trials” in a public database that would also publish results when the studies ended, as a *New York Times* editorial demanded.<sup>96</sup> Members of Congress have been introducing legislation along these lines in recent years, thus far with little hope of enactment.<sup>97</sup> A federal database that could post the trials, ClinicalTrials.gov, already exists; bills pending in Congress vary in their particulars, but all would require drug manufacturers to describe some large portion of their clinical trials on such a site before findings come in. This change in regulation

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93. David Bjerklie, *Drug Testing: Putting Trials on the Record*, TIME, July 5, 2004, at 42; see also Daren Fonda & Barbara Kiviat, *Curbing the Drug Marketers*, TIME, July 5, 2004, at 40.

94. Michael Gormley, *Drug Firm Agrees to Disclose All Data*, TORONTO STAR, Aug. 27, 2004, at F5.

95. See Rubin, *supra* note 88.

96. Editorial, *For Honest Reports of Drugs*, N.Y. TIMES, Sept. 11, 2004, at A14.

97. Drug Industry Announces New Initiative to Post Clinical Information Online, Kaisernetwork.org (Jan. 07, 2005), [http://www.kaisernetwork.org/daily\\_reports/rep\\_index.cfm?hint=3&DR\\_ID=27522](http://www.kaisernetwork.org/daily_reports/rep_index.cfm?hint=3&DR_ID=27522) (reporting on bills introduced in Congress).

would (again, in principle) bring information to public light.<sup>98</sup>

As with pharmacovigilance, the safety gains of this reform are obvious and the enhancements to effectiveness more hidden. Paxil-like findings about danger come to light, or at least become much harder to suppress, when a manufacturer has announced its study in advance. On effectiveness—the “new bottle” in which we propose to house this venerable “old wine” proposal—recall that for most drugs the magnitude of response is small: so small that effectiveness becomes apparent only after detailed statistical analysis of the data.<sup>99</sup> The great reliance on statistical analysis, in turn, creates a situation where missing innocent-looking information—excluding a few patients, say, for whom the drug did not work—can unseat the validity of the inferences. In other words, statistical tests operate on the assumption that the sample analyzed represents the underlying population. When some data are omitted, that assumption becomes incorrect.

Drug consumers (for this purpose, the physicians among them more than patients) who are willing to accept a chance that they will be fooled by randomness need to know about all trials conducted. A truly inert compound tested in a perspective double-blinded randomized trial has a one in twenty chance of demonstrating statistically significant results of efficacy: that, indeed, is the definition of the criterion for statistical significance,  $p = .05$ . If a pharmaceutical company conducted twenty trials of which only one found a statistically significant result, its

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98. At present the industry prefers to encourage postings on its own site, ClinicalStudyResults.org, which contains only those study results that manufacturers choose to disclose. See <http://www.clinicalstudyresults.org/home> (last visited Feb. 23, 2006). Its trade organization, the Pharmaceutical Research and Manufacturers of America, has defended its decision to limit the data that this site will reveal. *Id.* (follow “Clinical Study FAQs” hyperlink).

99. A notorious expression of how little actual response drugs deemed “effective” will cause came in 2003, when a senior executive of GlaxoSmithKline, the biggest pharmaceuticals company in Britain, announced that “most prescription medicines do not work on most people who take them.” Steve Connor, *Glaxo Chief: Our Drugs Do Not Work on Most Patients*, INDEP. (London), Dec. 8, 2003 at 1 (stating that “[i]t is an open secret within the drugs industry that most of its products are ineffective in most patients . . .”).

compound would not have been shown to be effective.<sup>100</sup> Consumers would be misled if all they knew about were the positive results.

Unburdened by an obligation to register its trials, a firm could hire twenty-five academic centers to study a useless drug, with none of the investigators being made aware of other studies. One or two of these trials would show a positive result, simply on the basis of randomness and the five percent statistical cutoff. These two studies could be submitted to a journal and published. Investigators so manipulated would argue with justifiable sincerity that they discovered something true and significant.

Even without bad faith of this kind, effectiveness will always be overstated when only positive trials come to public light. This overstatement increases because of a well-studied “publication bias”: medical journals disproportionately report findings of effects.<sup>101</sup> Researchers tend to submit, and editors tend to accept, studies that show “positive” results. Because negative trials are deemed less newsworthy, and are more apt to be methodologically flawed,<sup>102</sup> there are simply fewer of them in press. But

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100. For example, some randomized control trials seem to demonstrate the benefits of homeopathy, see Gregory M. Lamb, *Tracking the Idea Smaller Doses Have Bigger Effects*, CHRISTIAN SCIENCE MONITOR, Mar. 29, 2005, at 16, notwithstanding the pungent characterization of homeopathy as not only at odds with the tenets of medicine, but also in conflict with the laws of biology, chemistry, and physics. See ROBERT L. PARK, *VOODOO SCIENCE: THE ROAD FROM FOOLISHNESS TO FRAUD* 64-67 (2000); see also Robin McKie, *Sugar Pills That Cost Too Much*, OBSERVER (London), Mar. 10, 2002, at 33 (summarizing scientific consensus against homeopathy). In other words, there have been randomized trials that demonstrated what scientists agree is false. That does not unseat experts' confidence in the randomized control trial; we know, a priori, that it will be wrong five percent of the time.

101. A clinical trial is six times or more likely to be published if the results are positive. Kay Dickersin & Yuan-I. Min, *Publication Bias: The Problem That Won't Go Away*, 703 ANNALS N.Y. ACAD. SCI. 135 (1993). For a lay summary of publication bias, see Robert Matthews, *Don't Believe Everything You Read in the Journals*, SUNDAY TELEGRAPH (London), Jul. 31, 2005, at 35.

102. The scientific method posits that one does not prove a negative but rather fails to prove a positive. Logicians speak of “negation as failure.” See David Poole, *Logical Argumentation, Abduction, and Bayesian Decision Theory: A Bayesian Approach to Logical Arguments and Its Application to Legal Evidential Reasoning*, 22 CARDOZO L. REV. 1733, 1738 (2001). A trial might be

consumers seek a full picture. The best way to ensure that they are not looking only at a highlight film depicting only exceptional results is for them to know about every trial.<sup>103</sup>

Here we return to the mandatory registration schemes that the *New York Times* and members of Congress have advocated. In our view, the most straightforward way to foster information is not to demand that all trials be registered (manufacturers have raised plausible concerns about excessive exposure of what might constitute trade secrets) but rather to issue rules saying that if a manufacturer wishes one day ever to use the information from the trial as part of a new-drug application, that trial must have been registered at its outset. The FDA might treat information from non-registered trials like the “[i]solated case reports, random experience, and reports lacking the details which permit scientific evaluation,” that are not considered.<sup>104</sup>

3. “*Would an Alternative Treatment (or No Treatment at All) Provide More Utility?*”: *Answers*. We have seen that the Food Drug Cosmetic Act permits the FDA to regulate comparative effectiveness, even though the 1962 legislative history might, in one reading, bar the agency from withholding approval of a drug on the ground that another treatment is better.<sup>105</sup> Under any reading of the legislation, the FDA has the power to foster information about utility. It should craft rules to answer the question at the heart of consumer choice whenever an alternative exists: *Should I choose this drug, or another drug instead, or no drug at all?* Our proposals below build on recent developments in federal drug regulation.

i. *Current Law and Policies on Comparative Effectiveness*. Comparative effectiveness is already in play, wherever federal law and policy acknowledge that some drugs outperform others and that the public benefits from measures that elicit information about comparative drug

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“negative”—that is, fail to prove a positive assertion—because the positive assertion is false, or alternatively because it did not enroll enough subjects.

103. Highlight films obscure, for example, the fact that Reggie Jackson struck out nearly five times for every home run he hit.

104. 21 C.F.R. § 314.126(e) (2004).

105. See *supra* notes 44-50 and accompanying text.

performance. The first significant federal-government effort in this area came in 2003, when an \$80 million government-funded study yielded a point about comparisons that could save consumers billions of dollars: diuretics for high blood pressure, a drug category that has been entirely off-patent for decades, slightly outperformed the newer categories, like calcium channel blockers and ACE inhibitors, in which several drugs still enjoy patent-monopoly protection.<sup>106</sup>

The Agency for Healthcare Research and Quality (AHRQ) has declared that evaluating the comparative effectiveness of drugs within categories falls within this mission.<sup>107</sup> The Medicare Prescription Drug, Improvement and Modernization Act of 2003<sup>108</sup> directs this agency to conduct new research on “the outcomes, comparative clinical effectiveness, and appropriateness of healthcare items and services (including prescription drugs).”<sup>109</sup> This directive goes beyond the comparative effectiveness of drugs and opens up all treatments, including nonpharmaceutical ones, for comparison. So, in late 2005, the AHRQ issued its first report comparing treatments for a condition (gastric

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106. Goozner, *supra* note 82, at A23.

107. Health plans, hospitals, and Federal, State, and local officials are wrestling with questions about which drugs are most effective and how to balance costs with providing the life-saving benefits that medicines offer. Understanding which medicines work the best for which patients and at what costs, as well as understanding how to administer and monitor medication use in a way that ensures patients' safety, is of critical importance to the health care system.

Agency for Healthcare Research and Quality, *Pharmaceutical Research Highlights*, <http://www.ahrq.gov/news/focus/phrmhigh.htm> (last visited Sept. 7, 2006).

108. Pub. L. No. 108-173, 117 Stat. 2066 (2003).

109. 42 U.S.C. § 299b-7(a)(1)(A)(i) (2000 & Supp. III 2003). The legislation authorized \$50 million for this research, although to date federal budgets have not funded it. In 2004, the mandate of the Medicare statute to expand federal-government studies of comparative effectiveness won a big boost when Mark McClellan moved from heading the FDA to heading the Centers for Medicare and Medicaid. McClellan had been a longtime advocate of gathering data on effectiveness and cost-effectiveness, and his new post gave him a platform to continue “leading the charge for more cost-effectiveness information about prescription drugs” in a way that would keep up the pressure on the FDA to do the same thing, even with McClellan away from the agency. Jill Wechsler, *Looking for Value, The Push is on to Get FDA to Assess the Cost-Effectiveness of Drugs*, PHARMACEUTICAL EXECUTIVE, May 1, 2004, at 38.

reflux) along with promises for more reports in the future.<sup>110</sup>

In other comparison-gathering by the federal government, the Department of Health and Human Services has since 1997 sponsored a consumer satisfaction survey of managed care plans called CAHPS, which is "part of a nationwide effort to give employers and their workers a more objective way to buy coverage on the basis of quality, not just price."<sup>111</sup> The survey relies on questionnaires that private employers and state Medicaid providers distribute to patient-consumers. These respondents judge their health plans in response to questions that ask what fellow-patients would want to know: Do you receive the referrals they need? Have you felt respected and well-treated? How helpful is the information you receive? How long must you wait for service?<sup>112</sup> In principle, if not always in reality, consumers have access to these government-gathered rankings, and can use them when choosing among a menu of plans.<sup>113</sup> Although CAHPS does not (yet) survey consumers' experiences with drugs, it offers a blueprint for government-funded consumer comparisons of health care.

Comparative-effectiveness policies turn up elsewhere in government. The United States Department of Defense measures comparative clinical effects and comparative effectiveness; so does the state of Oregon for its Medicaid formulary. While the federal government does not yet

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110. See Press Release, Centers for Medicare & Medicaid Services, Statement of Mark B. McClellan (Dec. 14, 2005), <http://www.cms.hhs.gov/apps/media/press/release.asp?Counter=1739>. The AHQR moved into numerous studies of therapeutic alternatives used to treat the same condition. See Agency for Healthcare Research and Quality, *Effective Health Care: Topics in Progress*, <http://effectivehealthcare.ahrq.gov/synthesize/activeCER.cfm> (reporting on ongoing studies that compare the effectiveness of treatments for a dozen common conditions, including arthritis, cancer, and depression).

111. Joe Rojas-Burke, *Portland-Area Workers Rate Managed Care*, THE OREGONIAN, Feb. 1, 1999, at A1.

112. See *id.*

113. Four years ago, a news story criticized the intelligibility of CAHPS data offered to the public. See Glenn Howatt, *Health Plans Do Their Own Diagnosis, Say They're Doing Well*, STAR-TRIBUNE (Minneapolis), Nov. 13, 2001, at E2. The site does indeed seem oriented toward managed care organizations and the researchers who study them rather than patients. Nevertheless, we did find the site more accessible when we returned in March 2005, about six months after our first visit, and somewhat improved further in the following March.

publish overt comparisons of prescription drugs, its Agency for Healthcare Research and Quality maintains a website offering treatment guidelines that detail options for providers. It could readily expand this venue to include drug comparisons of the kind now offered in Britain's ministry, the National Institute for Clinical Excellence.<sup>114</sup>

ii. *Extensions of the Precedents: Toward More Information.* Legislation under consideration in Congress takes up comparative effectiveness as a regulatory necessity. One bill would require the National Institutes of Health and the Agency for Healthcare Research and Quality to undertake comparative studies of all drugs "that account for high expenditures or high use in federally funded health programs."<sup>115</sup> Democrats and Republicans have signed on.<sup>116</sup> The bill is not novel in that it tracks the existing Medicare Modernization Act authorization of this research; rather its contribution is to add money. Its Congressional sponsor has claimed to offer "trustworthy, evidence-based information [that] would be easily accessible (through Internet sites and publications) to private physicians, clinicians, patients, policymakers and the general public."<sup>117</sup>

The next stage of legislation could help finance the production of such information by taxing drug manufacturers' research and promotion budgets to finance comparative study of generic drugs.<sup>118</sup> Again, a precedent

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114. Amy Tsao, *Better Info, Cheaper Drugs?*, BUS. WK. ONLINE, Sept. 10, 2003, [http://www.businessweek.com/technology/content/sep2003/tc20030910\\_9672\\_tc078.htm?chan=search](http://www.businessweek.com/technology/content/sep2003/tc20030910_9672_tc078.htm?chan=search). Britain has pioneered in comparative effectiveness regulation through its single-payer National Health Service. See Wechsler, *supra* note 107 (noting that, in Britain, a drug manufacturer must provide information on comparative cost and value before its drug can be approved by the national service).

115. Rep. Tom Allen, *States Becoming Labs for Health Spending Reform*, THE HILL, Feb. 25, 2004, at 21.

116. See Tsao, *supra* note 114.

117. Allen, *supra* note 115.

118. Generics raise complex policy issues. See, e.g., Amy Barrett, *Biotech Drugs: Where Are the Generics?*, BUS. WK., May 9, 2005, at 98 (noting that biotech drugs cannot be replicated with the same degree of identicalness as other drugs); *E.U.'s New Drug Law Toughens Data Exclusivity, Delays Generics*, GENERIC LINE, Jan. 14, 2004 (reporting political controversy of the term). For present purposes, we accept what one pharmaceuticals lawyer has called a

informs our next level of rulemaking. Recall the triumph of diuretics when studied in comparison with newer, more expensive antihypertensive medications.<sup>119</sup> It is certain that other generic drugs provide an affirmative answer to *Would an alternative treatment provide greater utility?*, but this answer remains buried because drug manufacturers have inadequate incentives to seek it, while other researchers— independent nonprofit centers or FDA advisors—seldom look. Present R&D to support pharmaceutical innovation yields only partial information—only the data a manufacturer needs to determine whether going ahead is likely to become profitable—and leaves undiscovered the value of an innovation in context.

The information is missing in two senses: not known, and not shared when known. In February 2005, the respected nonprofit Consumers Union began an initiative to tackle the latter aspect. Consumers Union set out to supply comparative-effectiveness information via the Internet, thereby suggesting what further regulation would achieve. Its website offers comparisons of drugs in categories, offered as a growing database: when it launched its site, Consumer Union announced that it intended to cover “most of the commonly used prescription medicines in the U.S. today” by early in the next year.<sup>120</sup> The site provides “another perspective on the comparative value of prescription drugs—a perspective not driven primarily by pharmaceutical industry advertising and marketing that emphasizes newer (and more costly) drugs.”<sup>121</sup>

New rules could readily augment this crucial information-furnishing function by compelling manufacturers to learn—rather than closing their eyes to, and sometimes misstating—how well or poorly their new products compare to existing pharmaceutical treatments for a given condition. Because the drug market provides

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“simplistic definition” of a generic drug: “one which does not need to demonstrate that it is safe and effective for its intended use, that demonstration having been made by another party’s product.” Alvin J. Lorman, *Debate Over “Generic Biologics” Poses Unique Challenges for Policy Makers*, LEGAL BACKGROUNDER, May 14, 2004, at 1.

119. See *supra* note 104 and accompanying text.

120. CONSUMER REPORTS, *Best Buy Drugs*, FAQs, <http://www.crbestbuydrugs.org/faqs.html#2> (last visited Sept. 7, 2006).

121. *Id.*

adequate incentives for each manufacturer to study its own products, regulation should require manufacturers to compare their proprietary drugs with their nonproprietary competition, generics. Studies of generic beta-blockers give these treatments extremely high marks,<sup>122</sup> suggesting that valuable information would emerge through study of other treatments for high blood pressure, and still more through study of generic comparators for all proprietary drugs. New-drug applications should be revised to require inclusion of this comparative data.<sup>123</sup>

To further answer *Would an alternative treatment provide more utility?*, manufacturers of proprietary drugs might be compelled to pay for advertising to promote generics. Reduced to a slogan, the rule would be “Promote Nexium, promote Prilosec too,” a reference to the actions of one manufacturer, AstraZeneca: When its \$6 billion Prilosec, a proton-pump inhibitor used to treat heartburn,

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122. See CONSUMER REPORTS, *Best Buy Drugs, Treating High Blood Pressure and Heart Disease—The Beta Blockers*, [http://www.crbestbuydrugs.org/drugreport\\_DR\\_betablockers.html](http://www.crbestbuydrugs.org/drugreport_DR_betablockers.html) (last visited Sept. 7, 2006).

123. For comparable suggestions, see Goozner, *supra* note 82 (proposing that the FDA demand “comparative clinical trials for any new drug that a company wants to bring to the market.”); Angell, *supra* note 10 *passim* (proposing that the FDA withhold approval of new drugs that add nothing extra to the market); *supra* note 44 and accompanying text (reporting proposal from Jerry Avorn that the manufacturer of any drug not known to add value to its predecessors be compelled to disclose this information on its label). Within this genre, our proposal is modest: at this point, we recommend mandatory comparisons between a new drug and generics, not between the new drug and all its competitors; moreover, we do not seek information for the purpose of withholding approval, but rather to bring forward new knowledge along with a new drug.

Nevertheless, from the vantage point of manufacturers, this proposal is this Essay’s priciest suggestion, and we make it mindful of its costs. Our premise—shared by Angell, Avorn, and Goozner—is that any new drug entering a market that has strong competitors is less likely, *ceteris paribus*, to add utility than a drug that sets out to do something novel. If drug manufacturers feel that a regulatory demand for comparative data discourages them from launching their latest proton-pump inhibitor or beta blocker, so be it. Diverting their efforts toward producing and marketing more beneficial drugs would be consistent with the safety-and-effectiveness mandate. Peter Meredith, *The Truth About the Drug Companies*, MotherJones.com, Sept. 7, 2004, [http://www.motherjones.com/news/qa/2004/09/09\\_401.html](http://www.motherjones.com/news/qa/2004/09/09_401.html) (last visited Sept. 9, 2006) [hereafter *Angell Interview*] (noting that the drug manufacturing sector is “free to choose to make whatever drugs it wants to make. If it wants to make one more me-too drug, it’s free to do that instead of making an antibiotic that may really be needed.”).

approached the end of its patent life, Astra Zeneca created and marketed a new product, Nexium, which was almost identical to Prilosec and was no more effective. Nevertheless, AstraZeneca touted Nexium to both patients and physicians as better, reaping \$3.9 billion in Nexium sales during 2004.<sup>124</sup> "Nexium is a game that is being played on the people who pay for drugs," said the director of the Center for Medicare and Medicaid Services in response to this ploy,<sup>125</sup> and soon AstraZeneca faced liability for fraud.<sup>126</sup>

New regulations compelling the promotion of generics would not eliminate every game that a me-too drug manufacturer could play,<sup>127</sup> but would force competition against cheaper effective drugs on a more level playing field. Rule-writers can choose among alternative paths to underwriting the cost of promotion. In one approach that we favor, the federal government would tax manufacturers' research budgets to finance research into generic alternatives, and tax promotion budgets to finance promotion of what this research finds.<sup>128</sup> Independent

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124. Richard Sine, *Nexium Sales Increase 20% in 2004*, NEWS J., Mar. 31, 2005, at 7B. Prilosec went off patent in 2002 and became available over the counter in 2004. In 2004, Nexium cost more than five times as much as Prilosec. Alex Berenson, *Where Has All the Prilosec Gone?*, N.Y. TIMES, Mar. 2, 2005, at C1.

125. AstraZeneca Frequently Asked Questions, Hagens, Berman, Sobol Shapiro, LLP, <http://www.hagens-berman.com/files/Nexium%20FAQ%20FINAL%2021098987097439.html> (last visited Sept. 9, 2006).

126. The European Commission fined AstraZeneca sixty million euros for illegally blocking generic competitors and withholding material information from patent offices, a penalty that observers regarded as low. *AstraZeneca to Appeal 60-Million-Euro EU Fine; Analysts Shrug Off Impact*, AFX INT'L FOCUS, June 15, 2005. In late 2004, consumer plaintiffs, led by the AFL-CIO and senior-citizen-based nonprofits, brought an action in Los Angeles court against AstraZeneca, alleging that its promotion of Nexium violated California deceptive-practices law. Steve Niles, *New Direction for DTC*, MED AD NEWS, Feb. 1, 2005, at 4.

127. For example, a shortage of Prilosec on store shelves in 2005 provoked accusations that AstraZeneca, manufacturer of both, was withholding Prilosec so that patients would buy its expensive replacement. See Berenson, *supra* note 124, at C1.

128. Here we deflect the difficult question of what constitutes the promotion budget. In an interview, industry critic Marcia Angell remarked on the fine line between studies and marketing:

nonprofits like the Oregon Health and Science University could oversee the comparative research; private-sector advertising agencies could write and place the ads for generics, following the model of industry-funded advertising about the dangers of smoking.<sup>129</sup>

Assigning a portion of the industry's research and promotion expenditures to the study and promotion of generics puts only a modest burden on the private sector, and does not necessarily entail their financing of their own doom: While studies showed that generic levothyroxine, diuretics, and over-the-counter heartburn medication either equaled their name-brand competitors or outperformed them, other studies in the future might well find inequality and inferiority in generic drugs.

#### B. "What Is It Like to Consume This Drug?": Answers

Drugs differ from one another in how well they fit in this query. The safety/effectiveness tradeoff discussed above reappears: What is it like, one might ask rhetorically, to experience postexposure prophylaxis, a notoriously unpleasant treatment, after being bitten by a rabid animal? Answer: It's better than the alternative.<sup>130</sup> Some patients

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Well, no one knows for sure what goes into the R&D budget, because the companies aren't telling. It's been estimated that about a quarter of it is spent on Phase IV clinical trials, many of which are just excuses to pay doctors to prescribe the drug. They don't yield any real scientific information. But no one knows for sure.

*Angell Interview*, *supra* note 123. It would be prudent for new regulations to define promotion conservatively at the onset, perhaps with reference to the gifts that pharmaceutical employees give physicians.

129. Following a master settlement agreement that large tobacco companies signed with state governments in 1998, the cigarette industry has been paying for anti-smoking advertising. The rather sinister-sounding Citizens Commission to Protect the Truth, an organization funded by the master settlement to ensure that this advertising continues, includes as members "all the former U.S. Secretaries of Health, former U.S. Surgeons General, and former Directors of the U.S. Centers for Disease Control and Prevention—Republican and Democrat from every Administration over the last forty years." Citizens' Commission to Protect the Truth, <http://www.protectthetruth.org> (last visited Sept. 9, 2006). A blue-ribbon pharmaceutical lineup like this one could safeguard the promotion of generic drugs, a similarly urgent public health concern.

130. It is almost impossible to survive rabies without postexposure prophylaxis. A 15-year-old living in Wisconsin made headlines by recovering

will not complain about pegylated interferon-alpha plus ribavirin, its nasty side effects and high cost notwithstanding, because it is the most effective available treatment for chronic hepatitis C.<sup>131</sup> The question grows more revealing when patients have options among indicated prescription-drug treatments or where the consequences of making a therapeutically suboptimal choice are not dire: that is, when a drug affects "lifestyle" more than survival.

Under present regulation, the notion of a "lifestyle" prescription drug lives in twilight: half codified, half denied. On one hand, the concept fits intuitions about a drug hierarchy: on top are life-saving medicines; lower down are drugs that make a person's life more pleasurable by such effects as growing new hair or increasing sexual satisfaction; not much higher, to some observers, are reducing weight, enhancing mood, warding off pregnancy, and combating infertility. These intuitions are enforced. Formularies often refuse to pay for, or otherwise will discourage consumption of, drugs they deem inessential, cosmetic, or not central to the patient's health. Neither private insurers nor government insurance programs like Medicaid and the Veterans Administration are obliged to pay for every FDA-approved drug: they may discriminate among these products.

On the other hand, indicators reveal resistance to the dichotomy. Congress, for instance, used Medicaid amendments to force state governments to pay for Viagra, the first erectile dysfunction drug, and a handful of states have imposed the same mandate on private insurers.<sup>132</sup> Later the Centers for Medicare and Medicaid Services

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from the disease (with significant neurological injury), in response to treatment that she received a month after being bitten by a rabid bat. See Sharon Worcester, *Protocol That Saved Life of a Rabies Patient Requires Further Study*, FAM. PRAC. NEWS, July 15, 2005, at 24.

131. See *Liver Gene Profiles Signal Patient Response to Hepatitis C Therapy*, HEALTH & MED. WK., July 4, 2005.

132. See Kim H. Finley, *Life, Liberty, and the Pursuit of Viagra? Demand for "Lifestyle" Drugs Raises Legal and Policy Issues*, 28 CAP. U. L. REV. 837, 847 (2000). One reason Congress made that call on Medicaid was Medicaid patients are mostly female, and another large proportion are children. Only ten percent are adult men. It assumed the mandate would be cheap. *Id.* at 848.

determined that Medicare would cover such drugs.<sup>133</sup> Successful demands for birth-control and infertility coverage suggest a fight against the sense of dismissal that “lifestyle” conveys. Drugs for nondisabling mental illness, allergies, and mild osteoarthritis also seem to straddle the divide.

On balance, the divide between lifestyle and therapeutic drugs expresses a valid distinction, even though a few hard cases will land on neither side, and even though many treatments that appear therapeutic strive to improve the patient’s lifestyle.<sup>134</sup> But what does the line divide? An answer to this question would shed light on what to do with the vexing adjective: “lifestyle” offends many,<sup>135</sup> but few

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133. Laurie Kellman, *Medicare to Cover Viagra, Similar Drugs*, ASSOCIATED PRESS, Feb. 1, 2005. Not every dose of Viagra falls under “lifestyle:” physicians occasionally prescribe it to treat heart enlargement caused by high blood pressure. *Id.* Covering erectile-dysfunction drugs under Medicare is far costlier than doing so under Medicaid, a much smaller program means-tested to insure the poor. *See id.* (quoting a taxpayer activist: “Asking Uncle Sam to pay for the romance of 76 million baby boomers will quicken the impending collapse of Medicare . . .”).

134. Consider, for example, cardiothoracic surgery, an extremely invasive technology that seems to cut much deeper than the hair and fingernails of “lifestyle drugs.” While such surgery sometimes seeks to rescue a patient from dying, at least equally as often it seeks to improve quality of life: i.e., ease of breathing, the ability to climb a flight of steps. Laser surgery to correct nearsightedness repairs a diagnosed pathology, but also can cater to vanity; one journalist has suggested that it ranks even lower than “lifestyle.” *See* William Saletan, *The Beam in Your Eye*, SLATE, Apr. 18, 2005, <http://www.slate.com/id/2116858> (arguing that surgery to make athletes’ eyesight better than 20/20 is cheating, comparable to using steroids). Similarly, even though erectile-dysfunction drugs are marketed to enhance lifestyle, they also bring patients into physicians’ offices and thereby generate diagnoses of untreated diabetes, heart disease, and high blood pressure. *See* Diane West, *Physicians Favor Drug Ads, Study Says*, DRUG STORE NEWS, Mar. 25, 2003. Furthermore, the notoriously ‘lifestyle’ Viagra started out life as a treatment for cardiac disease; its sexual side-effect surprised its manufacturer. Klein & Tabarrok, *Who Certifies*, *supra* note 13, at 60.

135. *See, e.g.*, Susan D. Haas, *Researchers Advancing Science of Growing and Removing Hair*, MORNING CALL, Nov. 7, 1999, at A25 (arguing: “Baloney. As if the bearded lady life style is some kind of choice.”). In an interview, James Love, a staunch critic of the drug industry and director of a consumer group founded by Ralph Nader, refused to condemn the drug industry for pursuing lifestyle drugs:

I don’t know how judgmental I want to be about these things. If I was a woman and I had a lot of facial hair, I would want a product. It’s not as

replacement terms broached have been catching on. One English journalist proposes "behavioral drugs,"<sup>136</sup> a term that omits too many cosmetics like depilatories and fingernail enhancements, and may also be over-inclusive.

Stepping into this breach, we propose "sapient drugs" as an alternative term. We invoke a longstanding secondary meaning of "sapient"—not "wise," that is, but pertaining to human consciousness and reflection.<sup>137</sup> This dividing line separates human drugs that might be useful also for other large mammals in a veterinary practice, on one hand, from drugs that human beings choose (for themselves or others) to express or underscore some aspect of the patient's humanity, on the other. Like most lines between *homo sapiens* and other mammals, this one is not perfectly clear, and, as with the "lifestyle" label, some products will land near the border. The phrase "sapient drugs" offers important advantages over "lifestyle drugs," however. It adverts to nobility rather than frivolousness in the human species, thereby refraining from gratuitous insult to patients who choose to consume these substances. At the same time, it challenges the undefended prestige of equally "lifestyle"-focused therapies that have escaped this label.<sup>138</sup> It also follows the injunction about first doing no harm: Managed-care formularies, both private and governmental, already put what they classify as lifestyle drugs on their lowest tier, and so a new label that minimizes the old reference to frivolity would be unlikely to cause their patients detriment.

New regulations for "sapient drugs" could recognize the category while understanding that it presents a continuum, blurred at the edges, rather than an absolute. At the center of the sapient category would drugs sold primarily by direct-to-consumer marketing, as well as new drugs likely

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high a priority maybe as a product for cancer, but nobody condemns people who make Nike sneakers because they don't cure cancer.

FRAN HAWTHORNE, *INSIDE THE FDA: THE BUSINESS AND POLITICS BEHIND THE DRUGS WE TAKE AND THE FOOD WE EAT* 277-78 (2005).

136. Joe Studwell, *Oh, Behave!*, FIN. TIMES, Jan. 24, 2004, *FTmagazine*, at 16 (stating "[s]ome argue that the terms 'lifestyle' or 'quality of life' drugs insult those who suffer from pathological conditions such as depression, schizophrenia, obesity or compulsive behaviour, so we will use the term 'behavioural drugs.'").

137. See 14 OXFORD ENGLISH DICTIONARY 472-73 (2nd ed. 1989).

138. See *supra* note 120 (giving cardiac treatments as an example).

to be so promoted. The group would include prescription drugs not necessary to sustain life or fend off a future significant adverse event like a heart attack. The purpose of codifying the label would not be to withhold third-party payments but to identify which subset of prescription drugs call for closer attention to the experiences of patients who consume them.

We offer two examples of prospective new regulation that would work with the sapient category to yield information of value to drug consumers. Because sapience stands on a continuum rather than an absolute end point, these new regulations need not be limited to a particular shortlist of prescription drugs, but their gains would emerge most sharply for a drug designed to be taken regularly or frequently, and that patients, physicians, and entity consumers agree could be lived without.

First, we propose that the FDA track and disclose prescription refill rates of sapient drugs. Today the pharmaceutical industry, for its own purposes, monitors prescription refills in detail.<sup>139</sup> Portions of the data it gathers are the public's business. The FDA could require that pharmacies report directly to the agency—and indirectly to the public—how often a consumer who tries a lifestyle drug comes back for more. Other consumers would benefit from knowing about this instance of voting-with-feet. Some share of refill data should be disclosed: of particular benefit to consumers would be to know how many patients, on record as refilling other prescriptions, chose not to buy more of a particular lifestyle enhancement. Such a patient has revealed herself to be alive and well enough to buy more drugs, and yet uninterested in buying any more of this one.

Second, we would expand existing measurements of consumer satisfaction by the federal government: government studies like the CAHPS survey could also ask about patient experiences with sapient drugs.<sup>140</sup> Patients'

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139. Cutting Edge Information, a consulting firm specializing in pharmaceuticals, prepared a report in January 2004 using some of this refill data and offered it on its website at \$2,995 per electronic copy. See <http://www.pharmadiseasemanagement.com> (last visited Aug. 29, 2006).

140. See *supra* notes 109-11. In August 2005, the *New York Times* ran a series of stories describing patients' encounters with the American health care

opinions about side effects, value for money spent, convenience, packaging and labeling, accuracy of advertising, how fairly the drug is covered by insurance formularies, and the like would benefit all of our “new consumers.”<sup>141</sup> American individuals, especially (but not limited to) those who are relatively young or affluent, will, in the near future, grow more comfortable with more of the commercial rankings that already inform their purchases. Functioning like the maligned-yet-appreciated response data now established—think Zagat restaurant ratings, eBay feedback numbers, Amazon.com reader-scored reviews—government-supported satisfaction data would help consumers, especially patients, when they contemplate buying this optional commodity.

#### CONCLUSION: IN PRAISE OF HINDSIGHT: THE FDA’S MISSION STATEMENT

The FDA’s mission statement challenges regulators:

The FDA is responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation’s food supply, cosmetics, and products that emit radiation. The FDA is also responsible for advancing the public health by helping to speed innovations that make medicines and foods more effective, safer, and more affordable, as well as helping the public get the accurate, science-based information they need to use medicines and foods to improve their health.<sup>142</sup>

American drug regulators, charged with “assuring the safety, efficacy, and security” of prescription drugs,<sup>143</sup> may wonder whether they are doing their job well. They know that drugs inflict injury; does injury connote lack of safety?<sup>144</sup> Drugs often fail to make patients better off, thus

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system. The accounts, most of them reporting distress, ran on the front page and would land regularly on the “Most E-Mailed Articles” list at nytimes.com, suggesting a high level of consumer interest in this feedback.

141. See *supra* Part II.A.

142. See FDA’s Mission Statement, <http://www.fda.gov/opacom/morechoices/mission.html> (last visited Aug. 29, 2006).

143. *Id.*

144. See *supra* note 4 (quoting the famous statement by Paracelsus that all substances are poisons).

showing lack of efficacy; they also often fail to live up to the claims on their label, demonstrating ineffectiveness. In the United States the track record of drugs on “security” (in the sense of resistance to tampering or contamination) is very good, but also flawed.<sup>145</sup> Perfection on each of the fronts seems not only unachieved but unattainable. What then does the safe-and-effective mandate mean?

The drug-regulation mission statement mentions three goals—safety, effectiveness, and information—that function together to generate the fourth goal, public health.<sup>146</sup> Yet drug regulation in the United States has proceeded as if the goals of regulation were separate. The first comprehensive legislation on drugs, enacted in 1906, addressed “security” by prohibiting the sale of adulterated or misbranded drugs and foods.<sup>147</sup> A safety mandate (which covers “security”) came next, in 1938. Effectiveness joined the statutory mandate last, in 1962. The two criteria always overlapped,<sup>148</sup> and today they can no longer be seen in isolation.

As two interdependent variables, safety and effectiveness give the measure of each other. They come together to yield utility or value. And so for regulators, “assuring the safety, efficacy, and security” of drugs means working to maximize the beneficial effects of drugs, making them as useful or valuable as they can be.

Changes in the market have caused safety and effectiveness to merge into one query in the years following the last major statutory change in 1962, when the Food Drug Cosmetic Act received its last major changes. Back in

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145. The FDA has promulgated rules to deter third parties from tampering with sealed drug packages. See 21 C.F.R. § 211.132 (2004) (providing that over-the-counter drugs must be sold with “tamper-evident” packaging). Despite longstanding FDA enforcement of anti-adulteration regulations, in 1982 one or more malefactors tampered with several packages of the pain reliever Tylenol, causing seven known deaths. James A. Henderson, Jr., *Product Liability and the Passage of Time: The Imprisonment of Corporate Rationality*, 58 N.Y.U. L. REV. 765, 780 n.63 (1983) (describing the immediate aftermath of this tampering); see also *Elsroth v. Johnson & Johnson*, 700 F. Supp. 151, 153 (S.D.N.Y. 1988) (reporting a tampering-related products liability action).

146. See *supra* note 140.

147. Pure Food and Drugs Act, Pub. L. No. 59-384, §§ 6, 8, 10, 34 Stat. 768, 770-71 (1906), codified at 21 U.S.C. §§ 331, 351-52 (2000).

148. See *id.*

1962, demand came from only one cohort: the only people with power to choose prescription drugs were physicians. In the ensuing years, patients and third-party payors joined the demand side of this market. These three post-1962 consumers perceive safety and effectiveness as ongoing issues, in play long after the FDA has made its gatekeeping decision to approve each drug as safe enough and effective enough to be sold. They see "safe and effective" in layers. Their baseline expectation is that a trustworthy agency has approved the drug as adequate on these two criteria.

At the next layer, they need to know more. For consumers, safety and effectiveness cannot be achieved without information. Accordingly, the FDA mission to "speed innovations"<sup>149</sup> extends beyond the pharmaceutical laboratory and into its own rulebooks. Only innovative regulation of the kind we presented can fulfill the information mandate of the Food Drug Cosmetic Act.

Information about any prescription drug is unbounded, and so this Essay sorted what consumers want to know into categories. A first question asks about safety, the oldest area of regulatory concern. Consumers ask: How safe is this drug? Because the FDA's mandate is so famous and popular, many consumers know that at a point in the past extensive safety data supported approval, but they also understand that post-marketing experience alters the data once supplied in a new-drug application. Neither the Food Drug Cosmetic Act nor its regulations define safety, suggesting that the designation is fluid enough to change after marketing.

Another question: Would an alternative treatment, or no treatment at all, provide equal or more utility? Although a determination of effectiveness, unlike safety, rests on extensive definitional material in the statute, post-marketing experience also alters the earlier investigational findings of effectiveness—even more, perhaps, than safety. All the "new consumers" hope to choose the most valuable option on the prescription drug menu; not everything approved as "safe and effective" will be of equal use to them. Finally: What is it like to consume this drug? In broad terms, then, our reconception of "safe and effective"

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149. See *supra* note 140 and accompanying text.

works with three cohorts of consumers who have recurring questions.

Having emphasized the ground held in common among our new consumers, we now conclude with a few words about differences among the groups as they pertain to our "information prescription." All the cohorts ask similar questions. Each takes a particular interest in one or two.

For patients, the fourth question, "What is it like to consume this drug?" holds particular urgency, whereas physicians and entities ask it only instrumentally, as a means to anticipate compliance and therapeutic effect. Asked to name the uppermost question, a physician will likely mention safety. From its ancient Hippocratic pledge to "first, do no harm" through contemporary training about defensive medicine and the need to report adverse incidents, this profession worries foremost about the risk of inadvertently hurting another human being through well-intentioned medical treatment. An entity will take particular interest in questions about effectiveness and comparative effectiveness. More than the other two groups, entities regard prescription drugs as commodities with price tags, and they seek to maximize the therapeutic effect that each dollar will buy.

The groups also diverge with respect to the types of information they can best use and the harmful effects that information given to them can cause. The vast category of "patients"—essentially, all of us—contains a wide range of sophistication, literacy, ability to pay for desired products, and attitudes toward information. At one end, some patients want to know nothing about the drugs they take. At the other end, some cannot get enough information. Accordingly, the information menu for patients must be large and varied. As a starting point we applaud much of the FDA website, which presents updates about drugs in divergent levels of medical detail.<sup>150</sup> The danger of

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150. See FDA Home Page, <http://www.fda.gov> (last visited Aug. 29, 2006). It also can obstruct their care. One oncologist began a newspaper letter by reciting his credentials and then, after this recitation, lamented that "almost daily, I am in the position of defending my treatment recommendations against the cumulative results of several hours of Google-searching by a patient. . . . [This response] would be insulting if it were not so poignant and heartfelt." Marc L. Demers, M.D., Letter to the Editor, N.Y. TIMES, Aug. 18, 2005, at A24. Resolving the social-science debates about information overload—including

information, for patients, is that they will get too much of it. Information overload, to the extent it is a real danger (a question this Essay cannot answer), may cause them anguish.<sup>151</sup>

For physicians, our information prescription notes their training in evidence-based medicine. This focus on data is now standard in curricula research journals and clinical practice.<sup>152</sup> Trained to value information-based expertise over the opinions of expert individuals, physicians can and should learn promptly what epidemiological techniques reveal about the effects of particular drugs. The danger of information for physicians is a variation on the theme of information overload.<sup>153</sup> Now busier as a group than they have ever been, physicians lack time to absorb all the evidence-based lessons available about the drugs they can prescribe.<sup>154</sup> Like the social-science problem of information overload, the problem of how to give a doctor enough hours in her day lies beyond what this Essay can resolve. We note that our information prescription would have the secondary effect of reducing the noisy clutter that fills clinical practice today. Taxing promotion budgets to pay for promoting generics, for example, could well encourage a manufacturer to curb its marketing—and physicians are still, direct-to-consumer advertising notwithstanding, the major targets of this paid-for noise.<sup>155</sup> The obligation to register drug trials

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whether it exists—is beyond the scope of this Essay. We note only the possibility of danger.

151. For a summary of the dispute in both the law reviews and social science journals, see Michael S. Jacobs, *Toward a Process-Based Approach to Failure-to-Warn Law*, 71 N.C. L. REV. 121, 142 n.91 (1992).

152. The term dates back to 1992. Brandi White, *Making Evidence-Based Medicine Doable in Everyday Practice*, FAMILY PRACTICE MANAGEMENT (Am. Acad. of Family Physicians, Leawood, Kan.) Feb. 2004, available at <http://www.aafp.org/fpm/20040200/51maki.html#2>. See generally Joseph Bernstein, *Evidence Based Medicine*, 12 J. AM. ACAD. ORTHOPAEDIC SURGEONS 80 (2004) (summarizing developments in research and medical education).

153. See *supra* notes 149-50.

154. See *supra* note 150 and accompanying text.

155. See *supra* note 126 and accompanying text (proposing that regulators tax promotion budgets); notes 84-85 and accompanying text (discussing the high proportion of promotion budgets that go to reach physicians, the rise of direct-to-consumer marketing notwithstanding). See generally Posting of Katrina Vanden Heuvel, August's Big Pharma Scandals, <http://thenation.com/blogs/edcut?bid=7&pid=14841> (Aug. 20, 2005) (remarking that "doctors have gotten

similarly might reduce the number of such studies, eventually offering physicians leaner and more accurate data.

Entities, which buy drugs as commodities rather than to penetrate their own bodies or to fulfill a professional ethic of cure and care, would find that information will make purchasing decisions both more health-producing and more cost-effective. The benefits of sharing prescription-drug information with these entities have already emerged.<sup>156</sup> On the danger side, one might worry about augmenting corporate heartlessness.<sup>157</sup> An entity determined to get away with delivering as little as possible to fulfill its health-care contracts might interpret our focus on “information” as the opposite of compassion, patient autonomy, humane attitudes toward experimental treatment, or the possibility of granting discretionary exceptions to cost-cutting measures. We not only disavow

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dinners, vacations and even thousands of dollars in fees from drug companies to attend “conferences” and “summits,” where they are informed of the benefits of the wonder drug du jour.”). These promotions take up physicians’ time. *See id.* (reporting “In 2002, one cardiologist told the *Washington Post* that Merck sent a limo to pick him up, take him to dinner and included a bottle of champagne for kicks.”).

156. Private entities have been both selling and giving away such information to an enthusiastic consumer base. One nonprofit has presented a protocol, the Format for Formulary Submissions, to be used by pharmacy benefit managers. *See supra* note 15. The *Format*, which focuses primarily on scientific data showing efficacy and only secondarily on cost data to determine which drugs should be approved in managed-care formularies, is posted on the Internet for anybody to download and use. *See id.* A nonprofit consulting business called RxIntelligence has offered “independent, objective information comparing the costs and effectiveness of pharmaceuticals” to a subscriber base of employers, biotechnology firms, HMOs, hospitals, prescription benefit managers, benefit consultants (working with corporate human-resources departments), as well as pharmaceutical companies that wish to keep an eye on their competition. *See* RxIntelligence, <http://www.rxintelligence.com> (last visited Sept. 10, 2006); *see also* <http://www.rxintelligence.com/benefits/index.htm> (last visited Sept. 10, 2006).

157. *See* Avorn, *supra* note 10, at 368 (identifying two ends “of the pharmaceutical continuum: manufacturers who tend to see any new patented product as God’s gift to medicine whatever its price” on one side, and “insurance industry cost containers, who could have an opposite bias against costly new advances” at the other). Although his remark sounds critical, Avorn seeks to praise, finding value in the money-saving predilection of third-party payors. *See id.* (suggesting that in the United States, many organizations share the tasks of comparing drug cost and effectiveness, consistent with an American belief that “our nation’s strength has been in its pluralism”).

such a message: we have also shown that more information can resist it.<sup>158</sup>

Information to build drug regulation through hindsight holds promise. It guides interpretation of the Food Drug Cosmetic Act.<sup>159</sup> It responds to the questions that consumers ask about safety and effectiveness.<sup>160</sup> It fosters autonomy, a distinct good independent of public-health improvement.<sup>161</sup> The vast majority of Americans who now consume, will consume, or pay for prescription drugs can obtain from information the enhancements to drug safety, effectiveness, efficacy, and cost-effectiveness that they pursue.

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158. For example, we identified patients as producers and contributors, not just consumers, within the information-fostering endeavor. We endorsed consumerism as an avenue toward attaining more valuable drugs and we urged the FDA to heed patient-made information, including their records of refilling or not refilling their prescriptions. In addition, we see information as a tool for patients to fight unfair managed-care decisions that unreasonably take away treatment options. *Accord* Faye Fiore, Los Angeles Times Interview: Henry Waxman, L.A. TIMES, Nov. 9, 1997, at M3 (reporting an agenda among members of Congress to promote managed-care disclosures—from insurers to patients, physicians to patients, and insurers to physicians—as a means to improve public health).

159. *See supra* notes 4-22.

160. *See supra* Part II.

161. *See* Martha C. Nussbaum, *Flawed Foundations: The Philosophical Critique of (a Particular Type of) Economics*, 64 U. CHI. L. REV. 1197, 1204 (1997) (emphasizing the valence of autonomy: individuals “do not typically view as equivalent two states of the world, one produced by their own agency and the other not.”).