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TO YOUR HEALTH

Nudging the FDA

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There's a better way between the contending libertarian and paternalist approaches to regulating drugs.

Should terminally ill patients have access to drugs that have not been yet been approved as effective but have been shown in preliminary stages to be safe? Should doctors be allowed to prescribe drugs to patients for unapproved indications, uses for which they believe the drug will work but for which no drug trials have yet been conducted? Should drug companies be able to communicate directly with patients? All of these questions are at the heart of the proper role for the government in drug regulation.

The United States Food and Drug Administration (FDA) regulates about a quarter of the U.S. economy. Among its many responsibilities is the regulation of roughly \$275 billion in yearly sales of drugs, both prescription and over the counter. Although the FDA's role in drug regulation is frequently perceived as focusing on just a few actions—most notably, the approval or rejection of new drugs and the possibility of recalling drugs from the market based on safety concerns—it exercises many other powers that affect how drugs reach doctors and patients, and the information they receive about the drugs they prescribe and take. It also controls the accelerator and brake pedals on drug development and innovation through its control of market exclusivity for approved new drugs.

The FDA's regulation of drugs is frequently the subject of policy debate, with arguments falling into two camps. On the one hand, a libertarian view of patients and the health care system holds high the value of consumer choice. Patients should get all the information and the drugs they want; the FDA should do what it can to enforce some basic standards but should otherwise get out of the way. On the other hand, a paternalist view values the FDA's role as an expert agency standing between patients and a set of potentially dangerous drugs and potentially unscrupulous or at least insufficiently careful drug companies.

We lay out here some of the ways the FDA regulates drugs, including some normally left out of the debate, and suggest a middle ground between libertarian and paternalistic approaches focused on correcting information asymmetry and aligning incentives.

How the FDA Regulates Access to Drugs

The FDA is the undisputed gatekeeper of the U.S. drug market. No drug may be marketed or sold in the United States without FDA approval, and approving new drugs is among the FDA's most public and well-known roles. Approval of a major new drug, or refusal to approve a promising drug, garners news headlines and drives changes in drug company stock prices. The process of winning approval is hugely complex and expensive, even once a drug's clinical trials have demonstrated that a drug is safe and effective. The company that seeks to market a new drug (in the FDA's parlance, the drug's "sponsor") must submit a New Drug Application that typically spans thousands of pages of data and analysis. Clinical trials for new drugs take more than six years on average, and the FDA approval process itself adds more than a year on average. At the end of this lengthy process is a stark decision: The drug is approved, or it is not. Accordingly, and understandably, much debate about the FDA's role in regulating drugs focuses on the approval process.

In addition to the central gatekeeping function of allowing market access for a new drug, the FDA uses a wide array of tools and processes to regulate the way companies make and sell drugs; how doctors can prescribe them; and how patients are advised to take them. Several are worth pointing out; some are well characterized, but others are more nebulous. All are implicated by the ongoing debates about the FDA's role in balancing the safety of drugs against their potential use in treatment.

In a function tightly tied to the FDA's role as a formal gatekeeper in approving New Drug Applications, the agency regulates how and when clinical trials take place. The FDA approves the different phases of clinical trials, which test for safety and efficacy in human subjects, and determines what sorts of trials will be permitted. The FDA's formal approval of different stages of drug development thus reaches back much further than final approval.

The FDA also acts as an informal gatekeeper throughout the entire process of drug development. Drug manufacturers know what the FDA looks for in applications, what kind of drugs have trouble generating sufficient safety data, and what kinds of clinical trials might be viewed as problematic. As a result, "[o]ut of fear of rejection or stringency at the FDA, sponsors abandon hundreds if not thousands of new therapeutic ideas every year."¹ For instance, after the Vioxx scandal, in which Merck's top-selling painkiller was discovered to cause serious heart problems, the FDA requested major studies of heart effects for many similar drugs. The FDA also required much higher levels of statistical certainty for certain types of clinical trial results, especially those that prompt the early ending of clinical trials. Regardless of whether such requirements are justified, it means that a company with limited resources is much less likely to pursue those drugs, and will instead choose other research avenues.

The FDA also exercises significant power over whether drugs can be made available to acutely ill patients before the drugs are approved. Since 1987, the FDA has allowed companies to provide drugs to some patients who cannot participate in clinical trials before those trials are complete, if several criteria are met: no other treatment exists, benefits outweigh the risks, and providing the drugs won't compromise the clinical trial process. Typically, it is not possible to satisfy these criteria before drugs reach the final phase of clinical trials. Even in those cases where the requirements are satisfied, some have argued, the procedural hurdles involved in getting the FDA's permission can be substantial.

Patient advocates have chafed at the FDA's restrictions, and have challenged them in court without success. For example, consider the story of 19-year-old Abigail Burroughs. She was diagnosed with head and neck

cancer in 1999 and tried chemo and radiation therapy without success. On her physician's recommendation she tried to enroll in clinical trials for two drugs in development, etuximab and gefinitib, but was denied entry because she did not meet the inclusion criteria. In 2001 she was able to enroll in a third clinical trial but died soon into the trial.

Her father then created the Abigail Alliance for Better Access to Developmental Drugs, a group of parents of children with terminal illness. In the leading case, *Abigail Alliance v. von Eschenbach*, the Alliance sued the FDA, claiming a constitutional right to access drugs that had cleared Phase 1 of clinical testing (which focuses on toxicity) but had not yet been approved. Their claim was that the FDA's decision to restrict access by making the sale of unapproved drugs illegal was state action that violated these patients' right to be free from deprivations of their life or liberty without due process of law. (Full disclosure: One of us represented the FDA in parts of this case.) After achieving initial success before the Federal Court of Appeals for the D.C. Circuit, a full bench of that Court rejected the Alliance's claims, allowing the FDA to continue to block access to these drugs until approval. The FDA retains the ability to restrict the distribution of drugs during clinical trials and actively exercises this form of control over drug access.

Once a drug is approved, the FDA can require stringent restrictions on how and to whom a drug is prescribed through a procedure called Risk Evaluation and Mitigation Strategies (REMS). Under the Food and Drug Administration Amendments Act of 2007, the FDA can require that companies implement any of a broad set of measures to ensure that drugs are prescribed in specific ways to avoid risks. These range from merely requiring the distribution of a medication guide with the drugs to requiring doctor's certification about the use of the drug, requiring that patients enroll in a centralized registry, or requiring that the drug only be dispensed at specific specialty pharmacies. Notably, the Office of the Inspector General found in 2012 that although the FDA has imposed REMS on more than 200 drugs, it still lacks a reliable way to determine whether they are working. Nonetheless, REMS provide a potent way for the FDA to exercise tight control over the way new drugs are used.

Later in a drug's life (typically well after the patents covering the drug and protecting it from competition have expired), the FDA may, at a manufacturer's request, permit a drug to change from being prescription-only to being sold over the counter. This potentially creates much larger markets for drugs, since over-the-counter drugs typically have much lower costs than their prescription alternatives (because patients can buy them without visiting a doctor). Since insurance coverage usually requires a prescription, companies make up for the price decrease through vastly increased volume. To justify the shift, a drug company must demonstrate to the FDA that the drug is "safe and effective for use by the general public without seeking treatment by a health professional." Over the past twenty years, more than 700 drugs have made this switch, including the allergy medications Claritin (loratidine) and Allegra (fexofenadine), and the acid-reducing drugs Prevacid (lansoprazole) and Prilosec (omeprazole). On the other hand, the FDA has rejected many proposals to make the switch, such as Merck's request to make its cholesterol-lowering statin, Mevacor (lovastatin), available without a prescription. Statins have been available over the counter in the United Kingdom since 2004.

Finally, the FDA can remove a drug from the market entirely, typically when new safety concerns arise once the drug is in wide use. The FDA has the statutory authority to order a recall and withdraw a drug's marketing approval, but this step is usually unnecessary; most companies will withdraw a drug from the market upon the FDA's request.

The FDA's drug approval process not only affects access in this very direct way, but more indirectly by calibrating the pace and incentive of drug discovery and development. The longer, more expensive, and

more uncertain the pathway to approval, the less likely drug companies are to take a chance on a drug that may fail to show results or may face difficulties securing intellectual property protection. Further, the design of the pathway also strongly influences the corporate ecology of drug companies and issues such as mergers and acquisitions and the focus on blockbusters. Drug companies need to be a certain size to navigate the shoals of this process and have a portfolio of drugs in development that can capture enough market share to cross-subsidize the many drug failures.

The FDA's control over access to drugs is not limited to the physical drug itself. It also exerts potent forms of control over the information that is distributed about drugs, both to doctors and to patients. It has stringent rules about what drug companies can tell doctors about the drugs they sell. In general, drug companies are prohibited from promoting unapproved uses of drugs (even though a large fraction of prescriptions are for such off-label uses). The FDA can subject drug company employees, executives, and the companies themselves to civil fines or criminal prosecution for this behavior. The FDA has historically been quite strict about off-label promotion; in the past decade more than twenty settlements have been reached with drug companies, most for hundreds of millions of dollars. Five settlements for more than \$1 billion have been reached in the past five years alone, including GlaxoSmithKline's \$3 billion settlement in 2012 and Pfizer's \$2.3 billion settlement in 2009.

This strong prohibition of off-label promotion has recently been weakened. A 2012 decision by the U.S. Circuit Court of Appeals for the Second Circuit (which hears appeals from Federal cases in Connecticut, New York, and Vermont) cast doubt on the FDA's ability to criminally prosecute drug company representatives for promoting off-label uses of drugs. The case, *United States v. Caronia*, considered whether the First Amendment prohibited the FDA from criminally prosecuting a drug company representative promoting a drug's off-label use.² Specifically, Alfred Caronia told an FDA informant doctor that Orphan Medical's drug Xyrem could be used not only for its FDA-approved uses, but also for treating insomnia and other medical problems. The government brought criminal charges against Caronia (and others, who settled). The appellate court held that the First Amendment protected Caronia's speech, and that his speech was at the heart of the charges against him; therefore, the court overturned Caronia's conviction. The court still left room for the FDA to charge companies for fraudulent speech or marketing drugs they intend for off-label use, rather than attacking promotion directly. In addition, the FDA could still prosecute promotion directly in the 92 percent of the country not governed by Second Circuit law. Companies have not yet jumped on the First Amendment bandwagon, and several have settled off-label promotion claims after *Caronia*, including Johnson & Johnson's \$2 billion settlement in November 2013.

In addition to the information given by drug companies to doctors, the FDA regulates the advertisements displayed directly to consumers on television, the internet, the radio, and in print media. The United States is nearly unique in allowing this sort of direct-to-consumer advertising; New Zealand is the only other country to permit it. Drug companies currently spend around \$3 billion yearly advertising directly to consumers, the majority of which is concentrated on a relatively small number of recently approved, top-selling drugs. This was not always the case. Drug company advertising in non-print media increased dramatically after the FDA in 1997 relaxed its previously stringent requirements about the amount of cautionary information required to be included in advertisements.

Under current law, for an advertisement to be acceptable, it must disclose the major side effects of the drug and must give the consumers ways that they can find more information about the drugs by phone or through the internet. This accounts for the bizarre, almost surreal character of these television ads, which seem to come out of nowhere to describe vague, unfamiliar ailments that we are told we might have, and to promise that some strangely named therapy can help us—but which then go on to list a large number of invariably

serious side effects.

The FDA also regulates the types of claims that can be made about drugs; companies are not permitted to make false or misleading claims. The FDA exercises this authority with some difficulty, however. It frequently takes months for FDA reviewers to evaluate an advertisement, find it problematic, and communicate problems to the sponsoring company. In many cases, by the time the FDA informs the company about the problems, the ad campaign has already run its course.

Libertarians vs. Paternalists

One major attack on the FDA and its regulation of drugs comes from a philosophical core we loosely describe as “libertarianism.” That term means different things in different contexts (for example, it carries with it one connotation in debates about free will and another in debates about taxation). In the context of objections against the FDA, it begins with the premise that ordinarily individuals are the best judge of their own interests, and that when the state tries to substitute its judgment for that of the individual in a way that is one-size-fits-all the state will most likely get it wrong. Second, this power of the individual to make his or her own choices is most important when it comes to control over the body. The *locus classicus* here is the work of John Locke. It is a basic necessity of freedom, of being a person, that a person be in control over his or her body, a sovereign, a self-owner, and from this are derived the ownership of property and all other accouterments of modern citizenship. Third, that control over one’s body is particularly salient when one is trying to protect one’s life, for without one’s life this freedom is meaningless. Thus, the right to defend oneself, a right older than Blackstone, is often crowned preeminent among the rights enjoyed by individuals.

Even with this bare-bones articulation, it is clear that these principles collide with *any* regulation of drugs. To see this, take the issue of access to experimental drugs that was front and center in the *Abigail Alliance* case. The terminally ill individuals who brought suit claimed that they were willing to take the risks for a chance at recovery or extending their lives, and that they were better judges about the risks and benefits involved than the FDA. They claimed that it was up to them to decide what to do with their bodies. They also argued that the constitutional right they claimed to have in this case was analogous to self-defense, or, in the words of one prominent legal academic, “medical self-defense.”³

There is a similar clash between libertarian principles and the FDA’s regulation of direct-to-consumer advertising and off-label drug promotion. Libertarians argue that it should be up to individuals, on consultation with physicians, to decide whether a particular use of a drug is appropriate for them. Indeed, in some ways the cutting off of information by the FDA is more threatening to them in that the FDA is seeking not only to regulate what individuals put in their bodies but what information they may consider in their minds.

In the opposite corner philosophically are a group we might call “hard paternalists”, though the group is somewhat heterogenous. Sometimes, some argue, the evidence weighing against a particular choice is so strong that individuals cannot be permitted to make that choice. This rationale most clearly underlies the FDA’s entire structure of market pre-approval. Under the 1962 Kefauver Harris Amendment, the FDA may not approve a drug for marketing unless it determines that the drug is both safe and effective, no matter whether consumers might like to buy it or not. Sarah Conly and George Rainbolt have written more recently justifying this form of “hard” paternalism in the requirement that certain drugs be available by prescription only.⁴

There is also a related but separate argument in favor of FDA regulation. While paternalist arguments

typically focus on protecting the individual who would take the drug, some have also justified FDA regulation on behalf of benefits to others. One argument scholars offered for the FDA policy at issue in *Abigail Alliance* was that allowing the purchase of drugs outside of clinical trials would greatly delay recruitment for those clinical trials. The end result was that it would take much longer to approve these drugs or determine that they were ineffective, and that many future users would suffer because of this delay. So on that basis it was argued that it is necessary to channel terminally ill patients into clinical trials and not make the drug available to them outside of those trials.⁵

Information Asymmetries and Nudges

Hard paternalism is not the only potential response to the libertarian attack on FDA regulation, nor is it the most effective one. Rather, one can accept but qualify the basic libertarian premises of self-ownership and that individuals are the best judges of their own welfare. According to a well-established political theory tradition, individuals can only make good choices when they have good information. In this view, regulation of the channels of information is a prerequisite for exercising meaningful choice, not in conflict with it. The combined activities of the FDA and the Federal Trade Commission can be defended, then, as attempts to prevent the misleading of consumers.

Second, the regulation of information and, indeed, access to therapeutics is particularly justified in health care because of the strong information deficit faced by consumers. As Nobel Prize-winning economist Kenneth Arrow famously argued in the 1960s, individuals have a very hard time evaluating health care's value to them. Health care is often conceptualized as a "credence good" by economists because patients cannot verify the effectiveness or quality of a treatment. They may have gotten better because of treatment, they may have gotten worse because of the treatment, or the treatment may have had no effect. Even well-educated experts often cannot know which is the case, and so most patients clearly have a limited ability to evaluate the effect of the treatment and almost no ability to determine causation.

The FDA's role is in part to correct this problem. It determines which drugs work by evaluating the data provided by pharmaceutical companies, and allows those companies to advertise the drug only for the indications for which it has determined the drug to be safe and effective. Without these safeguards, some would argue, drug companies would not have the incentive to conduct expensive clinical trials, many of which fail. Instead drug companies might prefer a market for drugs that resembles the one we have for vitamins and other supplements, a free-for-all where anyone can enter, advertise, and sell without proving the safety or efficacy of the product.

One can combine this qualified defense of paternalism from a philosophical perspective with a qualification of the level of paternalism of the intervention. In particular, recent work in behavioral law and economics has emphasized two milder forms of intervention: "asymmetrically paternalistic" interventions or "libertarian paternalism" in the form of "nudges."

Asymmetrically paternalistic interventions create "large benefits for those who make errors, while imposing little or no harm on those who are fully rational."⁶ "Nudges", on the other hand, set default rules (among other approaches) so they can "influence behavior while also respecting freedom of choice."⁷ Those default rules may be sticky—that is, they take some effort to change—which means that those with a strong preference can overcome the stickiness and change the outcome, but those without strong preference will leave the choice set at the socially optimal level. Combining these two vectors of "soft paternalism"—mandates to provide accurate information so that the patient's choice is indeed informed, along with asymmetric or libertarian paternalist behavioral interventions to set patients on the socially optimal route

while preserving freedom to choose—would provide something of a middle ground for the FDA to consider before it uses the “big guns” of “hard paternalist” mandates. We can recast some policy choices the FDA already makes in this light, but this also suggests new possible pathways for the agency.

The FDA’s strict regulation of the quality and veracity of drug information for patients makes sense under this framework since good information is a prerequisite for meaningful choice. Similarly, we can conceive of the rules governing the substitution of generic drugs for branded drugs along these lines. The socially optimal policy is to prefer broad substitution of generic drugs, because they are much less costly and by definition have the same effect. However, the system can still preserve consumer choice, if doctors can specify that a prescription be filled with the branded drug, which creates a sticky default for the socially optimal choice. Those with strong preference for their preferred branded version may get it (albeit at a higher cost and requiring the intervention of a doctor).

And what might new FDA policies treading this middle ground look like? The universe of possibilities is vast, but here are three suggestions. It could require prescriptions or create other “speed bumps” to accessing drugs prone to abuse, but not completely block access. Patients who overcome these speed bumps are more likely to be informed or have intense preferences, while those who do not can be channeled toward what is determined to be the socially optimum policy. Second, it could require patients to exhaust conventional therapies and demonstrate that they cannot get into a clinical trial of an experimental drug, but then allow them to purchase it outside of the clinical trial regime. Third, it could allow drug companies to make available information about unapproved uses, but require multiple procedural steps to obtain that information, such as individually initiated registration and a waiting period.

These are just the tip of the iceberg, and FDA policymakers could certainly formulate many other, more sophisticated approaches of this kind. Not every policy choice is amenable to this middle ground, of course. In particular, these considerations are unlikely to be useful for those FDA actions that shape the behavior of firms rather than the access of consumers, because firms are typically sophisticated rational actors without the same magnitude of information asymmetries or cognitive biases. These ideas are also presented as thought-provoking possibilities, not as fully defensible proposals.

But even to engage in this form of creative regulation the FDA itself may need a nudge. The FDA is used to using the blunter tools of approval and prohibition. Those tools are baked into the agency’s organic statute and generations of practice. Moreover, the FDA has considerable incentive to use the more restrictive tools available to it since it is usually the first to be blamed when something goes wrong, but receives little praise when it permits patients to get what they want. One legacy of our colleague Cass Sunstein’s tenure at the Office of Information and Regulatory Affairs is the introduction of choice architecture and soft paternalist approaches into government regulation. Even libertarians should prefer soft paternalism to the hard sort the FDA is prone to use. With that in mind, we encourage libertarians and paternalists interested in the FDA’s mandate to consider whether these new, “nudged” forms of regulation might satisfy both constituencies, at least in part. We think they can.

¹Daniel Carpenter, *Reputation and Power: Organizational Image and Pharmaceutical Regulation at the FDA* (Princeton University Press, 2010).

²See C. Boyden Gray, “Free Speech: What the Doctor Ordered”, *The American Interest* (July/August 2013).

³See Eugene Volokh, “Medical Self-Defense, Prohibited Experimental Therapies, and Payment for Organs”, *Harvard Law Review* (April 2007).

⁴Conly, *Against Autonomy* (Cambridge University Press, 2013); Rainbolt, “Prescription Drug Laws: Justified Hard

Paternalism”, *Bioethics* (January 1989).

⁵See Ezekiel J. Emanuel, “Cancer in the Courts”, *New Republic*, July 3, 2006.

⁶Colin Camerer *et al.*, “Regulation for Conservatives: Behavioral Economics and the Case for ‘Asymmetric Paternalism’”, *University of Pennsylvania Law Review* (2003).

⁷See Cass R. Sunstein & Richard H. Thaler, *Nudge: Improving Decisions About Health, Wealth, and Happiness* (Penguin Books, 2008).

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