

## **Introduction to the Italian Edition of *Overdose*<sup>1</sup>**

By Richard A. Epstein,

*James Parker Hall Distinguished Service Professor of Law and Director, Law and Economics Program,  
University of Chicago Law School; Peter and Kirstin Bedford Senior Fellow at the Hoover Institution*

It is my very great privilege to write this introduction to the Italian translation of my book *Overdose*, which has been prepared by the Bruno Leoni Institute. It is entirely appropriate that the Institute should have undertaken this task, for the message of this book is perfectly congruent with the enduring mission of the Institute. First, the market issue: we both seek to improve social welfare through the active expansion of markets in the many areas of life where this approach proves appropriate. Second, the safety issue: we agree that no activity is riskless but that people should be allowed to take those risks that they deem worthwhile so long as they are not misled by other parties. Both these issues are central in the unending battle over the proper scope of regulation of the pharmaceutical industry. I discuss both in detail in this volume, chiefly from the American perspective. This introduction will address how these two issues play out in international arenas, especially in the EU, including of course Italy. Let us take them up in turn.

### **Matters of Pricing and Market Structure**

#### **Why Markets?**

Writers in the US and the EU who are in the libertarian tradition do not agree on all matters. But they all accept that, on matters of economic exchange, the major function of the state is to define property rights in

---

<sup>1</sup> *Overdose: How Excessive Government Regulation Stifles Pharmaceutical Innovation*, Yale University Press (2006).

goods and labor and to enforce voluntary exchanges in competitive markets to generate mutual benefits for all parties. That innocuous proposition is hotly contested today by critics who think that virtually all markets in which competitive solutions are proposed are plagued with “special” circumstances that require an ever-expanding menu of state regulation that limits the ability of individuals to fashion their own contracts. Labor and agricultural markets head the list; the result can lead to minimum wages in the former and price supports in the latter. But that list is infinitely expandable to traditional and newer markets, such as real estate and telecommunications. On both sides of the Atlantic, alas, a common complaint is that the provision of health-care services, including pharmaceutical products, is so distinctive an undertaking that it cannot be governed by these market principles but requires extensive regulation over all phases of business.

To evaluate this common claim, it is important to get a sense of what ordinary market principles require and how they apply to a (dwindling) class of “ordinary” industries. The initial assumption in favor of competition rests on one durable assumption about the dominant motivation of ordinary individuals. Starting with Adam Smith, if not earlier, the basic postulate is that most people, most of the time, tend to prefer their own welfare and that of their family and friends, to that of strangers. The case in favor of competition rests on the way in which it harnesses those impulses of self-interest without interfering with altruistic actions—charity, rescue—that individuals often take for the benefit of others.

Bargains that are reached in the marketplace generate win/win results, regardless of their price, terms, or conditions. Transactions will only take place if both sides, respecting their own self-interest, are believe that they will be left better off with the deal than they would have been without it. Viewed as such, these transactions are not sterile; they lead to increased value for all concerned. They will, moreover, be capable of generating larger gains if contracts can be enforced over time, so that one person can perform today secure in the knowledge that his trading partner will perform tomorrow. This theory of exchange is perfectly general, for the ability to specialize in the work performed and the products made and exchanged holds true across the board. State intervention thus harnesses self-interest in a way that works to the mutual benefit of the parties involved.

Nor are third persons slighted in this effort. As two individuals make each other better off, each has greater resources and skills to enter into contracts with third persons. The systematic externalities from the transactions are positive, for any losses to disappointed competitors are more than offset by gains to consumers and successful producers. The key role of the legal system is to reduce impediments to voluntary transactions. As that happens, the number of players who enter the market will increase, leaving those who are less efficient to exit the market or to reform their business strategies in order to succeed.

Any successful market system restrains individual misbehavior by a system of open entry. The seller who tries to raise prices above costs knows that someone else will seize the opportunity to offer the same goods at a lower price, while still turning a profit. Hence, to keep active competition on both sides of the market, two general prohibitions are put into place. The first of these is that traders on one side of the market are not allowed to collude with one another to acquire monopoly power, which would allow group members to reduce output and raise prices, thereby diminishing social welfare while filling their own pockets. The second is that buyers are not allowed to collude in order to lower prices below the competitive level, thereby reducing prices below competitive levels. These risks are symmetrical and both are to be avoided.

Typically, these voluntary efforts to collude fail because colluders cannot keep out new entrants that will restore market order. Nor can a cartel prevent its members from “cheating” on their collective solution by offering to sell below group prices or buy above them, as the case may be. It therefore follows that successful efforts at monopolization typically need state force to keep cartel members in line and to keep out new entrants. The danger and immorality of the use of state power to achieve this end should be evident. Members of the protected groups would be rightly condemned as mobsters if they threatened to use violence to prevent would-be competitors from selling their goods. Their actions do not suddenly become pro-social because their political clout allows them to get financed enforcement against potential competitors from the state taxpayer. The transformation of the state from the protector of private property and competitive markets into the architect of entry barriers is one of the great scandals of government.

## Pharmaceutical Patents

The basic argument carries over without a hitch into the many marketing issues that face the pharmaceutical industry. Just why is this industry to be regarded as special? One reason is that it depends on patented products, which create, it is said, a form of monopoly. But a moment's reflection should indicate why the point is a distinction without a difference. Many industries depend heavily on patents—or, if not patents, then copyrights and trade secrets. Yet in all these areas, great care is taken in the articulation of legal doctrine, in the US and the EU, to see that no piece of intellectual property dominates the entire field. Thus a common feature of all forms of intellectual property is acceptance of the proposition that no one can gain intellectual property protection for ideas (including general laws of science) or natural substances. These rules go a long way in preventing the accretion of blockade provisions through the preservation of an intellectual commons. As such, intellectual property is little different from physical property, which is also divided into resources that are private (such as land) and resources that are common property (such as air and many forms of water).

In practice, the right balance has to be kept between private and common property. In some instances, courts could go astray in ways that create property rights that affront our sense of individual autonomy. For example, the rule in the United States that allows for patent protection for “isolated and purified” substances was announced almost a hundred years ago by the great American jurist Judge Learned Hand, and it has stood the test of time in pushing forward on the genetic revolution. But like all principles, it can be misapplied. One current illustration deals with the isolation and purification of the BRCA genes that can trigger breast cancer. The current state of affairs in the US, but not in the EU, allows the patent holder of that gene to block any treatment at the gene site inside a person, given its work in isolation and purification. That rule seems to cut deeply into the ordinary sense of autonomous self-rule that is respected in any responsible social order and that appears to flout the general rule that natural

substances are ineligible to receive patent protection. The case illustrates what can go wrong in any complex system of property rights, but it is easily fixed without knocking down the entire edifice. All that is needed is a rule that extends the strong patent rules only to genetic material that is isolated and purified, with an eye for use or sale in that form, and not to the original material in one's own body.

It is important not to be overwhelmed by such errors, for no matter how marginal the cases come out, the basic rules of patents do not allow one to patent a receptor site for COX-2 inhibitors such as Vioxx or Celebrex. The exclusive right to sell a given product is consistent with robust competition as long as other products in the same class of drugs that serve the same function or act on the same bodily processes are also entitled to patent protection. The knowledge that new entry can erode the advantages of patent protection spurs inventors to get the *first* drug in class to market as quickly as possible. Yet for all the unhappiness about the monopolies created by patent production, it is better to have a single drug in class where none existed before and thus tolerate a short-term economic monopoly, than it is to have *no* pharmaceutical in a given class or for a given condition. Who would want to avoid the monopoly problem by having no innovations at all? The current system rewards the first comer with large rewards, but those rewards spur other parties to enter the same field, often with new drugs that are perceived as superior to those already in the field. Nothing about the need for complex patent production makes pharmaceuticals a field in need of special regulation, including regulation of prices at which drugs are sold.

The argument against price regulation of pharmaceuticals is further strengthened when it is recalled that all patent protection is for a limited duration not only in the US, but in Italy and throughout the EU. The new generation of patented drugs faces competition from the previous generation of patented drugs, which, once generic, is available at lower cost from multiple producers. There are real complexities in this area when the payment for medical treatment is controlled by third-party payers, which include private insurers as well as government agencies in the US and the large state-run systems in Italy and the rest of the EU.

The tricky choice for each user is whether to go generic. One concern is whether the production values of the generic product match those of the original patented product. If not, the price differential may not lure users of the patented product to its generic substitute. The deeper and more pervasive conflict lies in whether the new patented products should be regarded as superior to the now-generic product, so as to justify the cost differential. Here is a conflict of interest between the patient who receives the drug and the national health-care system, often strapped for cash, that must pay for it. Recent studies in the United States, Great Britain, and Japan indicate that health-care payers will occasionally understate the benefits of the newer treatment in order to continue to use the cheaper generic form—a conflict of interest that is not easily resolved in any public or private system.

### **Price Controls**

*On Manufacturers.* The inability to reach a definitive utilization on these difficult questions does nothing to justify common types of legal restrictions on the distribution of patented and generic drugs. The most dangerous is the disease of price controls, which is most evident in the market for new pharmaceutical products, where its consequences heavily affect the rate of innovation for new drugs. Such price controls for new drugs are particularly easy to impose in the EU, where the state is the sole or dominant purchaser of products and the pharmaceutical supplier thus has nowhere else to turn. The vulnerability of research pharmaceutical companies to price controls, moreover, is great because these governments know that pharmaceutical products have high fixed costs at the front end but low marginal costs for each additional pill. The pharmaceutical company knows that no one will pay the full cost of that first pill, so it must recover a portion of its front-end investment from each subsequent sale. But a state monopsonist can drive down the price close to marginal cost by refusing to pay much more, and it can back up that demand by threatening to invalidate the patent protection for any company that does not cooperate, which has

happened in Brazil and Thailand. It makes little sense for pharmaceutical companies to refuse these offers, for their fixed costs may then be recovered only over the fewer units that remain in the market.

The political problems become more acute because of the obvious disparities in price between high prices gathered in some sectors of the unregulated American market and the lower prices in many EU countries. Drug companies now face a chorus of protest from both sides. The American public insists that foreign countries pay their fair share of the development cost. Elsewhere, nations defend dramatic levels of price discrimination as a fair reflection of the differences in wealth across nations.

In facing these issues, complex market forces do a better job in setting prices, by allowing for some recovery of front-end costs, but not for the reasons that many Americans perceive. A common US mistake is to claim that the higher prices overseas will lead to lower prices in the US, as other countries shoulder a larger portion of the cost of innovation. But this behavior should be expected from any profit-making firm. Presumably, firms are pricing to maximize their profits within the American markets. As a first approximation, why should they give up any profits at home just because they make additional profits overseas? Subtle interactive effects may alter this calculation, but even if that happens, the chief source of gain to US consumers from higher prices outside the US comes not from lower prices for the same bundle of goods but from the availability of a better bundle of goods that follows from more rapid innovation. Any investment in patented products takes into account the potential returns in the global market. The higher prices overseas (since they are not offset dollar for dollar by lower prices at home) spur greater investment to tap into this more lucrative market.

Italy is no exception to the general EU penchant for unwise price controls on pharmaceuticals, especially for patent drugs. Alarmed by rising prices, Italy introduced in 1994 a complex regulatory “reference” price structure that in its initial form divided drugs into four categories: A, B, C, and H. Drugs for severe illnesses fell into category A. Other important drugs were found in category B. Category C included drugs that are not covered in either of the first two categories. Finally, category H was restricted to drugs that are supplied only through hospitals. Category B was formally abolished in 2002, leaving the

three other categories. Once drugs are thus categorized, Italy's system of reference pricing ties the price of any drug to a larger class of which it forms a part. These classes are intended to create the equivalences based on the nature of the active ingredients, form of delivery, dosages, and the like, and to set the price in each class equal to that for the lowest available generic price.

The purpose of the plan is to result in substitution of generic for nongeneric drugs unless the physician or patient objects. Oddly enough, this principle, which is meant to exert downward pressure on the market, may not lower generic prices. The critical determination may well be the initial price at which the generic drugs are offered for sale, for no company that lowers its price could expect compensation in the form of higher market share, given that it knows that its competitors will be forced to follow. It is therefore quite possible that individual companies now find it in their interest to keep their prices higher, knowing that they have nothing to lose by offering their drugs at a lower price unless required by law to make these price reductions. The various refinements on the system under the so-called jumbo plans, which look to identify the weighted daily average costs, do little to soften the problem, even if they may alter the prices for various drugs.

Any system of categories and reference prices does not reflect the usual market method of evaluation, which allows each purchaser to decide how much of his or her resources to devote to drugs in various categories. The reference prices are rigid and will never move higher, even for drugs that have advantages that were not revealed when they first came onto the market. Consumers are no longer price setters but are strictly price takers. Similarly, the lines between the four Italian categories may make sense in general, but the system of collective evaluation will necessarily generate major errors at the margins. Some drugs can be misclassified by simple error that is hard to correct. Other drugs may have multiple uses, which are vital for some patients but less critical for others. The restraints imposed by this system do not allow individuals or physicians to make adjustments based on their own private information. The bureaucratic imperative is at best constrained or informed by vague tests that speak globally of "clinical efficacy," "risk-benefit balance," or "acceptability."

Relying on these categories has the added drawback of setting up the dangerous dynamic whereby drug innovation is delayed as the single government provider squabbles with various suppliers over the desirability of particular drugs. That problem is frequently compounded by a reluctance to use new drugs in the first place, often on the unsubstantiated claim that they are no better than the cheaper, often generic, drugs that they displace. These misconceptions can lead to deadly delays. Recent comparative surveys have shown that survival rates from a wide range of cancers are higher in the US than in Japan and many EU countries precisely because new and better therapies are pressed into service more rapidly in the US than in the EU. The pricing policies that keep them out result in systematically higher mortality rates outside the US, where the available arsenal of drugs is more restricted. Consumers are aware of these differences, when given a choice to act on their preferences. In the US, for example, the various prescription drug programs available under Medicare Part D are driven more by market competition than by government fiat. Accordingly, the rival plans bid for customers by allowing them to choose from a larger formulary than is now available, for example, under the less expensive programs run by the Department of Veteran Affairs, which has been hailed as a model of fiscal prudence by advocates for greater government regulation.

But consumers have voted with their feet, deserting the cheaper programs whose choice is limited for higher-priced programs with strong access to new products. The object of market transactions is not to minimize cost, which would make it desirable to spend nothing at all on health care; it is to maximize the net gain from drug expenditures, which will increase, but only without price controls, as long as the added health benefits exceed the added costs of newer treatments, which they typically do. The situation is made only worse because of the tendency in the EU to find that pharmaceutical companies with patents have a “dominant economic position” that makes them vulnerable to regulation under the EU’s expansive competition policy, which, far more often than the comparable American antitrust law, enables national regulators to force incumbent patent holders to license their products to generic competitors without the receipt of royalty payments.

*On Retailers.* The situation with price controls is often no better on the retail side of the industry. In Italy, for example, the strong grip of the cartelized retail pharmacy industry on the distribution of generic and patented drugs limits the number of pharmacies, all because of the dubious social judgment that a political body can assume that one pharmacy for 4,000 individuals is the “right” number for the community. These ostensible judgments on the optimal shape of this industry do not tie back to the choice between generic and patented drugs, for the clogged distribution channels only raise the cost for consumers of both types of drugs. Far from speaking about the distinctive nature of patented products, the defense of this dubious institutional arrangement rests on the familiar protectionist arguments that other industries use to immunize their members from new competition. We are thus told that without these interventions, big distribution chains will enter the market and drive out the smaller ones. What is left unsaid is that the benefits to consumers from lower prices and greater product selection exceed the losses to the incumbent sellers, who must adapt to survive.

We can explain why countries outside the US are often so eager to impose price controls: they gain the full benefit of lower prices at home but bear only a small fraction of the global loss from delayed innovation. It is the US market that suffers a large fraction of the losses from the belated introduction of new products. But if EU members freeload in one respect, they cannot freeload in a second. No matter where a pharmaceutical company develops drugs, it has to decide where to introduce them first. The relatively unregulated American market now induces companies to open business first in the US, where higher prices allow for a more rapid recoupment of the original investment. Companies will introduce drugs into EU nations that are demanding low prices after the drugs have been established in the US and the cost of introduction has declined. In the long run, no one can know whether European countries benefit on net from their price ceilings, but they may. The price control tactics that they use can be turned against them when other nations imitate Thailand or Brazil by insisting on exceedingly low prices for public-sector drugs. These controls benefit the home nation but slow the pace of innovation for the US and the EU. Turnabout is fair play.

The European impulse toward price controls also resonates in the US market, as countless politicians insist that only price caps will restore parity with European prices. Nonetheless, the countervailing forces in the US are stronger than in the EU. Intellectual support for unregulated markets has greater intellectual resonance in the US than in the EU. Domestic US companies possess some political clout, and their dire warnings on price controls are not wholly unheeded. Domestic price controls have such a bad odor in the US that major efforts to cut prices are by indirection—to allow the reimportation of drugs that are delivered to countries outside the United States, especially Canada, for reshipment back into the United States at low Canadian prices.

The same principles apply to drugs manufactured in the US or elsewhere for the arbitrage opportunities opened by price discrimination regardless of the drug's national origin. Buy cheap in Canada for use or resale in the United States. This practice started on a small scale. People who lived near Canada traveled across the border to buy needed medications, and then brought them back into the US. But there are limits on how many domestic sales can be lost to these piecemeal purposes. The real threat to the US market comes only when intermediaries advertise sales in Canada for major shipments in the United States at prices below the unregulated US price.

This particular strategy has yet to bear fruit. Any business importer of goods from Canada knows that the first sale of an unauthorized drug within the US is an act of patent infringement. More important, the US Food and Drug Administration has not inspected these drugs or approved them for sale in the US, because of trade regulation and, more important, health and safety. On the former ground, the International Trade Court in the US is empowered to keep out misbranded or infringing goods. On the latter, the FDA in Democratic and Republican administrations has been adamant that the lengthened supply chains pose a health and safety risk from counterfeit drugs, whose use can be deadly. Proponents of parallel trade claim that these health risks are overstated, but the rash of counterfeited and dangerous goods from China has led many to question this optimistic scenario.

What is missing from the US debate is a serious appreciation of the massive market distortions that would remain even if, as is doubtful, the safety issues could be resolved. The proposed statutes are mind-boggling in their implications. In the name of free trade, drug companies that sell in the US will be forced to supply to drug resellers in foreign nations whatever quantities of drugs they demand at the price that the host foreign government sets for its purchases for domestic consumption. The quantities so purchased are, of course, destined for resale in the US. Once the drugs are brought back into the US, the proposed American legislation would strip all patent protection from the original holder. In effect, the domestic prices in foreign nations become the de facto price controls for American sales, in ways that could easily decimate the domestic market for the drug company's own product.

So far, the economic objections to reimportation have gained little traction in the US. But the adulteration risks have proved salient enough to stop the adoption of this ruinous proposal. How similar legislation in the future will play out is unclear. The EU has no monopoly on bad fixes for pricing in the drug industry. But amid all these regulatory initiatives to gain national advantage in the drug industry, two points should be stressed.

First, pricing should ideally take place in all markets as if no borders separated one nation from another. Some price discrimination will take place in these markets, given local and regional differences in demand, which depend in part on the available wealth in various market segments. (Ironically, if these drugs do wonders for people in poor countries, their poverty allows them to get the greatest health gains for the least amount of cash.) But those instances of price discrimination cannot be condemned as the impermissible consequence of government regulation that seeks to create a legal monopoly at home and whose adverse consequences are felt overseas.

Second, the greater understanding of price controls might lead, if only marginally, to more rational policies at home and abroad—or so we could hope.

## **Advertising**

In most markets, advertisement is taken for granted as a way for firms to introduce new products and maintain the sales of older ones. The practice works because of the powerful way in which brands hold their sellers hostage to the quality of their products. Businesses of all kinds invest large sums to build up brands to establish the trust of their customers. If the seller allows the quality of its goods to deteriorate, it will pay a heavy price: the brand will operate in reverse, by leading consumers to believe that other products made by the same seller suffer from similar defects. Hence, reputation is a powerful constraint that ensures that sellers sell the products that they promise; otherwise, customers will go elsewhere.

The additional costs of advertisement should not be regarded as a form of social waste, on the ground that consumers really want the product but not the hype and promotion. A key benefit of advertising is that it expands the scope of the market, so that the fixed cost of bringing a new product to market can be divided among a larger number of consumers, which makes it possible to lower the average cost of the new goods in question. As new sellers come into the market, they can provide stiff competition to the established players, which helps erode any dominant or monopolistic position of the first entrant into the market. The advertising business garners billions in revenue in the US and the EU and can amount to as much as a third of the total budget for a product. If these expenditures did not make sense, someone would cut them and sell more pills for less money. Occasionally, that happens; but in general, sellers follow the same rule with respect to advertisement as they do with all budget items. They quit when the additional dollar of expenditure does not garner an additional dollar of revenue, which is exactly what we want them to do.

Notwithstanding the powerful social justifications for advertisement, its use has been sharply curtailed in pharmaceutical markets, usually by appealing to the special nature of the market in question. One key difference between pharmaceutical markets and other products is that the efficacy of the goods often cannot be determined by inspection before use, or even by limited use. There are always questions of

the long-term safety and appropriateness of any product, especially any new product. But those information gaps do not point to stopping all advertisement; the question, as always, is whether the ad campaigns increase or reduce physician or consumer information. Most of the time, advertising closes the information gap and thus makes markets more efficient, not less. The notorious “detail men,” or drug promotion people who bring drugs to doctors, often receive a respectful hearing from their physician clients, usually because the drug reps know something about what the new therapies promise.

There are nettlesome conflicts of interest, but these rarely justify a ban on certain forms of advertising, given that they are commonly mitigated in at least two ways. First, all companies can engage in the practices so that no one pharmaceutical company has a monopoly on the market. Second, other players can enter the business as well, to present conflicting views on drug effectiveness. These other entrants include physician and advocacy groups of all stripes. In the end, this form of advertisement persists because physicians need the information. Better a little bias, if such there be, than no information at all.

Direct-to-consumer advertising (DTC) is prohibited in the EU. On this score, the situation in the United States is better, for DTC came of age in the US in 1997, when the FDA liberalized the requirements for these advertisements so as to make them a sensible economic proposition for sellers of prescription and nonprescription goods. The entry into the market has been intense; a decade later, it is estimated that \$10 billion is spent in DTC, with about 60 percent of it going through traditional print and media channels, and the remainder through the newer Internet and other communication networks. As with physician advertisements, critics of DTC are vocal but largely misguided. To be sure, the information supplied can lead patients to try drugs that they do not need. But in most instances, the greater danger is that persons without physicians, or with inattentive physicians, simply do not know that there are medicines that help eliminate the chronic conditions that make their lives unhappy or dangerous. The pluses have to be taken into account with the minuses, and the increased use of DTC has gone a long way in dealing with undermedicated populations. It is ironic that critics of the market system decry the limited access that many

people have to medical care, only to attack the private actions that, at no cost to the taxpayer, work to improve medical well-being. On matters of advertising, as on matters of pricing, beware of claims that the special status of pharmaceutical products warrants a new round of government restrictions. The older rules that used government to control coercion, fraud, and monopoly do quite well in this arena when suitably adjusted.

## **Health and Safety Issues**

As far as health and safety, there is room for sensible forms of government regulation under the traditional general police power of the state. The most obvious application of that truth comes from the law of tort, or delict, which has assumed similar form in Roman and common law systems. The first line of protection is the prohibitions against trespass and nuisance, which are directed against pollution and other noxious actions that threaten the health and safety of strangers and neighbors. In addition, the remedial difficulties of using private actions to police various harmful things, such as air pollution, result in public agencies often filling the gap to vindicate the private rights of ordinary individuals. These matters have no direct relevance to the pharmaceutical industry.

The situation is different with contractual norms on health and safety. Here the usual rule in common and civil law countries holds that any merchant seller implies that its products are those represented on the label and that they are sold in a form safe for human consumption, which includes freedom from adulteration and contamination. No buyer would accept products that fall below these rudimentary standards, which is why no manufacturer seeks to disclaim them by contract or to resist public regulations that are perceived to strengthen consumer confidence in the purity or uniformity of goods sold. A disclosure on a container of tuna or a bottle of pills that says “this container contains poison” is, in principle, allowable, but nowhere observed. Those who want to buy rat poison do not venture into

supermarkets or drugstores, so full and honest disclosure guarantees that the product will never reach the market. To the extent that the Food and Drug Administration in the US, or the EMEA in the EU, is directed toward this objective, the case for public regulation is at its highest.

There are many serious questions of how to best administer these programs to control against mistake and abuse, without turning them into arbitrary excesses of state power. After all, it has happened that unannounced inspections have shut down firms whose only sin has been to offer better goods at lower prices than an established competitor. Preventing the abuse of safety regulation for anticompetitive ends is a huge task for any sound system of public administration, but that political risk is not critical here. Quality controls in the pharmaceutical industry are astonishingly high, so recalls for bad batches of drugs by legitimate manufacturers are virtually unheard of. The problem with quality control is exclusively a problem of dealing with counterfeit goods, for which sound public regulation is needed to restore the confidence of consumers.

The discussion is transformed when it turns from contamination and impurities to the inherent risk of drugs that promise to benefit those who use them. Regrettably, the word “inherent” is appropriate in this context, because in the short term, redesign is not an option for most pharmaceutical products. As a legal matter, the new drug will have to go through a new round of clinical trials and receive a new regulatory approval. In some cases, the reconfiguration that eliminates one risk will promptly create another, which will be equally difficult to design out. No one should conclude from these remarks that the ratio of good to bad effects cannot be improved by careful research. Yet virtually all potent and state-of-the-art medicines carry serious side effects, including the risk of death and disability. But unlike poisons, these same medicines may also hold out the only chance of cure for a chronic condition or deadly disease. Since drug reformulation is not a viable short-term option, the only weapon left to improve individual choice is a full disclosure of the positive and negative aspects associated with the particular product. Given that some individuals will benefit on net, full disclosure will not lead to the withdrawal of a product from the market.

Instead, accurate information should help all individuals make rational choices on whether to use a particular drug.

How should this information be supplied to ensure its greatest net value? Can this information be privately supplied? Publicly supplied? Should individuals be allowed to act unilaterally on the strength of that information? The last is most important because the common negative answer to that question in all Western democracies means that public legislation has replaced individual choice, leading to the dangerous consequences against which Bruno Leoni warned: “If one values individual freedom of action and decision, one cannot avoid the conclusion that there must be something wrong with the whole system.” Nowhere is that more true than with access to valuable but dangerous pharmaceutical drugs. Information disclosure is the second issue on the agenda, which arises only after government agencies have approved the market for dangerous drugs. But it is never the first issue, such that the only questions that remain are who counsels, warns, and advises.

Why have all Western democracies decided to interpose a deep layer of state authority between individuals and drug use, between individuals and the professionals to whom they might turn for advice, not only on risks but also on benefits? The stated rationale is that it is too risky to potential consumers to allow the sale of a pharmaceutical product in the absence of a scientific showing that the medicine is safe and effective for its intended use in its recommended or standard dosages. The threshold decision on drug use has been taken out of the hands of the individual and put into the hands of the state, which now makes its own administrative evaluation on expected costs and benefits before allowing the product to reach the market.

The situation differs materially between the US and many countries in the EU, whose standards of review on these health and safety issues are less exacting—that is, more sensible—than those in the United States. The American rules are relatively free with respect to price but highly paternalistic with respect to safety and effectiveness, with insistent demands for extensive clinical trials costing hundreds of millions of dollars before a new drug can be let into the market at all. The situation has grave consequences for health

and safety around the globe. To the extent that these tests require more validation than individuals would demand when acting in their own capacity, they function as a tax on scientific research, raising cost and delaying the introduction of the regulated products. Some products will be proved worthless or dangerous through clinical trials; but this fact does not justify the use of state power to block individual choice.

Two pieces of compelling evidence show that government agencies are more risk-averse on clinical testing than the individuals whom they purport to represent. The first concerns drugs that have yet to reach the market. There is in the US a consistent pressure on the part of well-connected individuals to be allowed to use experimental drugs notwithstanding their evident dangers. The attitude of these drug seekers is, “What do I have to lose?” when all other therapies have failed to prevent the progression of a fatal cancer or other commission. It is not as though these individuals make their decisions without guidance. Quite the contrary; their pleas are routinely championed by their own physicians, who have concluded that desperate measures are required when all else fails. If this were a case where a deep-seated bias and sense of desperation deprived individuals of all their rational faculties, then the state might seek to regulate to prevent incompetent persons from hurting themselves. But those conditions are not there. The usual protection against individual competence is independent advice, which virtually all patients receive, from their family members and from their professional medical advisors. Here is a case in which private voluntary provision appears to work better than state systems of ostensible protection, which, in the typical one-size-fits-all model, are the same for the most and the least sophisticated members of the population.

The second piece of evidence is the extensive off-label drug use, especially in cancer cases. The practice arises only for those drugs that are already allowed on the market for a specified “indication.” Once there, the FDA in the United States does not have the power to regulate the practice of medicine, so physicians who have been frustrated on one front will take drugs that are licensed for one purpose and use them for a second. Typically, there are no clinical trials for the new target of treatment, just a combination of crude empirics, weak theory, and professional interchange. Again, it seems pointless to attack this extensive gray-market practice, when the alternative is passivity in the face of impending doom. It is not

cognitive bias or emotional instability that drives the new regime; it is the same answer, given before, to the question “What do I have to lose?” When the answer is “nothing,” a long shot is worth taking. We have strong evidence that the accretion of voluntary practices yields results that are both different from and better than those that follow the general pattern of government paternalism.

The extensive demand for experimental and off-label use should not be understood as an attack on the coherence or merits of clinical trials. No one would think that clinical trials should be banned because people resort to other forms of information in their absence. The basic trade-off is that when you have little or no time, you use unreliable information that is relatively easy to acquire, as long as it improves expected outcomes. If more expensive but more reliable information becomes available, behavior should adjust, not by disregarding the cumulative wisdom of day-to-day practice but by updating previous preferences in light of new information. Hence, the state should remain agnostic on the type and extent of clinical trials that are undertaken. Even if the state gets out of the business of monitoring new drugs, large and sophisticated buyers of health-care services will not simply accept on faith the safety or efficacy of an untested drug. One likely consequence of removing state regulation is a resurgence over private oversight of just these critical topics.

One reason that private oversight should be preferred is that it is decentralized so that multiple systems of review operate side by side, allowing for competition in the area of drug safety. Unlike state bodies, these groups are less likely to skew preferences so as to overweigh the institutional interest in keeping bad drugs off the market—out of fear that their adverse consequences will create a tremendous stir. Yet the forgone benefits of drugs kept off the market typically will not generate any form of public response unless, as is increasingly the case, disease groups organized on the Internet take a strong interest in the drug in question, as happened recently in the United States with Provenge, Iressa, and (in connection with the most severe warnings) Prozac. Even with these additional pressures, the differential responses to good and bad news remains, and thus leads safety agencies to become too cautious in their approval and warning processes.

A better response would be to cut back the state's role, perhaps entirely, in the licensing function so that risk-benefit analysis can be privatized in ways that match the sophistication and preferences of various potential user groups, many of which contain knowledgeable physicians and support groups with extensive experience in dealing with chronic and serious diseases. The danger is still greater because the losses from delay are compounded by the inherent variability within the user population. Treatments that are useful for some individuals are dangerous for others; a sorting mechanism has to be made on a personalized basis, even for drugs that obtain regulatory approval. The higher cost and longer time of working the appropriate clinical studies, moreover, alters the balance between Europe and the United States by shifting much of the research for new products to European theaters, which are more responsive to research needs than American institutions, which place powerful restraints on drug research, including that which is close to basic science.

No one can say that the risks of individual mistakes in using drugs that are ill fit for their purpose should be minimized, which is why voluntary markets (such as the National Comprehensive Cancer Network) seek to organize information about how various treatments work alone and in conjunction with others. Nor is the information confined to professionals. For example, iGuard ([www.iguard.org](http://www.iguard.org)) contains detailed ratings of all drugs on the market, accessible to laypersons and capable of being customized for individual circumstances.

We can therefore make this instructive generalization about the information shortfalls that are ever more common in complex products. As long as information is valuable, we should expect, without government intervention, voluntary organizations to gather and disseminate information to those who need it. Often information will flow through multiple channels at the same time, so physicians will receive technical information through journals, learned societies, and specialized websites. Sometimes distribution will be on a for-profit basis; in other settings, information will be provided through unpaid contributions of experts in the field, for reasons of public service as well as peer recognition. The cost of direct regulation in these settings is measured not only in blockades and delays but also in the weakening of voluntary

organizations to which greater resources would be devoted if they held a more central place in the distribution chain.

Any informed assessment on the comparative performance of American and European institutions requires detailed investigations by knowledgeable comparativists, which cannot be attempted here. Those results could easily differ by nation and by drug class. It is nonetheless possible to state issues that should be confronted in making apples-to-apples assessments of drug safety regulation between the US and the EU, which consolidates its drug approval operations in the EMEA (Agency for the Evaluation of Medicinal Products), which, since 1995, has been responsible for drug innovation for the EU. Data from the Tufts Center for the Study of Drug Development (a clear leader in the field) do not point to dramatic differences between the two systems, at least by one metric: the average time for obtaining drug approval. The medians in the two systems, as of 1999, were about 370 days for the EMEA and 366 for the FDA. That difference is too small to matter.

A striking difference was in the variance, which was far higher in the US than in the EU. But this ostensible parallel conceals other differences. Regulation of drug safety in the EU is not only by the EMEA but also by national agencies that are charged with the same tasks. It would therefore be instructive on the EU side to ask whether this second tier of evaluation is perfunctory or whether it delays the entry of new drugs into the market. In addition, the length of time through the process is not the sole measure of health effectiveness. More relevant is how quickly the drugs get to market, which depends in part on when pharmaceutical manufacturers choose to initiate the process—which depends on the pricing issues discussed earlier. A full evaluation depends on the level of reliance that various agencies can place on the work supplied by others. If the FDA approves drugs first, and its information is available to the EMEA, the process should be more rapid because there are more data to work with in the first place.

The operation of the two safety organizations may be influenced by other functions that they perform. Most notably, the EMEA or its national counterparts sometimes have control over pricing decisions as well as safety issues. For example, the equivalent of the FDA in Italy, AIFA, is responsible not

only for the safety evaluation of drugs but for decisions on entry, pricing, and state reimbursement. The formal separation of function within government offers some protection against dangerous linkages whereby the approval of one new drug might be delayed because of pricing differences on another. But it is always a concern that the informal backdoor communication could allow for retaliation on the approval side of companies that have resisted the price demands of regulators. Evidence on this question is difficult to acquire, so the issue now rests on suppositions about the nature of bureaucratic operations that could prove false in many cases but true in others.

There is little doubt that on the American side, this problem surfaced with large companies that had multiple products before the FDA for approval. The firm that publicly criticizes the FDA runs the risk that bureaucratic maneuvers will slow down the approval process on other products that it has before the FDA. None of the FDA's actions will appear on any public record, so the underground obstruction is likely to work. After all, no pharmaceutical company would risk delays on a dozen applications in order to criticize the FDA's delays on others. And no company would sue an agency to expedite the review of its own products, thereby creating the delay that it so strongly fears.

The issue of comparative competence thus merits further study. The only certainty is that the excessive faith in state regulation as a source of protection for individuals is a danger found in both systems, which means that drug innovation in both systems is likely to lag relative to what would be expected in more unregulated markets.

Any discussion of health and safety issues would not be complete without mention of the use of private litigation to advance these ends. In the US, litigation against drug companies is in full flower, as the state law courts have taken the position that information shortfalls from warnings are likely to be systemic, for which the only remedy is aggressive litigation by individual persons who claim that drug companies have deceived or misled them by incomplete disclosure of relevant information and overpromotion and advertisement of their products.

These charges of pharmaceutical malfeasance are very serious and have resulted in thousands of lawsuits—for example, those being filed against Merck, the maker of Vioxx, after it was withdrawn from the market in 2004. All these suits concede that Merck was in complete compliance with the FDA standards for warnings, which, if anything, can overstate potential risks relative to potential benefits. Ironically, this litigation proceeds on the assumption that the FDA is a “captive” agency that issues warnings that are too weak and never too strong. Unfortunately, litigation cannot correct biases within the FDA warning system. The damage that is done by delay, on the one hand, and alarmist warnings, on the other hand, cannot be corrected through litigation that reduces the burden of new drugs in the marketplace. But it is possible to compound the system by allowing for personal damage actions even when FDA warnings are complied with. Ironically, the FDA has moved on this issue. At one time, its view was that tort actions were a sensible addition to fill in the gaps in its own regulatory armor. More recently, the FDA has urged courts not to allow individual plaintiffs to second-guess its judgment on matters of safety but to use its warnings as complete defenses against any private lawsuit that claims that FDA-approved warnings were inadequate.

Developments on this front are likely to mystify Europeans, for whom the private rights of action under the tort law play, at most, a small role in the regulation of pharmaceutical markets. The impulse in favor of weak private litigation doubtless stems in part from the much greater willingness of European states to rely on administrative expertise to make key judgments on safety and health. It is possible to quarrel with that judgment because of the costs that state oversight imposes on individual choice; but whatever the response to the current regulatory situation should be in the EU, one transformation that should be avoided is the adoption of American tort law. It may be that neither heavy regulation nor private tort actions are intrinsically desirable, but on the matter of warnings, the choice seems clear. Once drugs make it to market, it is far better for an administrative agency to issue warnings that remove all tort litigation than to open the field to after-the-fact judgments that always attribute a greater weight to the

alleged defects in the warnings given than they had in fact. This is one swamp that the EU nations are well advised to avoid.

## **Conclusion**

All points referred to in this introduction, and many more, are developed in *Overdose*. One clear conclusion is that the theoretical and institutional issues in *Overdose* do not apply only within the American—or indeed, the common law—context. As a longtime (since 1973) teacher of Roman law, I am convinced that fundamental social problems are often driven by technology and not by variations in cultural norms across nations. Local forces often take the legislation in one nation in quite a different direction from what the legislation assumes in another nation. But the analytical framework that is used to evaluate proper modes of normative evaluation is remarkably stable across legal systems, even if the applicable legal rules vary substantially. Various proposals for the reform and improvement of the law jump across oceans and language barriers—which is why Bruno Leoni continues to have an audience in both Great Britain and the United States. I hope that the translation of *Overdose* sheds light on a set of important issues that now face Italy and the rest of the EU, and I am pleased that the Bruno Leoni Institute deems the lessons contained in *Overdose* are powerful enough to warrant this translation.