Rational Basis Review And FDA Regulation: Why The Two Do Not Mix

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Rational Basis Review and FDA Regulation: Why the Two Do Not Mix

RICHARD A. EPSTEIN*

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INTRODUCTION: SETTING THE STANDARD OF JUDICIAL REVIEW

It is a commonplace observation that most of the unresolved tension in American constitutional law has less to do with the nuances of particular substantive provisions and more to do with the standard of review that courts—the Supreme Court, most specifically—bring to any challenged government action, be it a statute, a regulation or an executive action. As commonly understood, the American constitutional world, like Gaul, is divided into three parts, in descending order of constitutional severity. Strict scrutiny, intermediate scrutiny, and rational basis form the basic triad. The higher the standard of scrutiny, the lower the probability that the government action will survive a judicial challenge. It should not be thought, however, that the three tests stand equidistant from one another, like one, five and nine on a number scale. In practice, intermediate scrutiny is a lot closer to strict scrutiny than it is to rational basis, like one, three and nine.

* Laurence A. Tisch Professor of Law, New York University School of Law; the Peter and Kirsten Bedford Senior Fellow, The Hoover Institution; and the James Parker Hall Distinguished Service Professor Emeritus and Senior Lecturer, the University of Chicago. This paper is prepared for a conference, “Is the Rational Basis Test Unconstitutional?” cosponsored by the Georgetown Center for the Constitution and the Institute for Justice’s Center for Judicial Engagement, held at the Georgetown University Law Center on February 11–12, 2016. The paper was discussed the day before Justice Scalia died, and it may well be the case that he would not have agreed with a single word of it. But I nonetheless belatedly dedicate it to the memory of a most extraordinary justice and human being. I should also like to thank Rachel Cohn, Philip Cooper, Julia Haines, Madeline Lansky and John Tienken of the University of Chicago Law School for their excellent research assistance. © 2016, Richard A. Epstein.
I shall not long tarry to give definitions of these three standards that capture every doctrinal nuance. That is difficult now that the standards have been so battered over time that they no longer remain in their pristine state. Thus it is no longer clear what strict scrutiny means in connection with affirmative action programs\(^1\) or what rational basis means in connection with gay rights;\(^2\) and those meanings differ from its use in such central areas as federal jurisdiction, economic liberties and property rights. Whatever the development on hot-button social issues, in these core areas it is the case that whenever the rational basis test is closely associated with the use of the word “conceivable”\(^3\) or “irrational,”\(^4\) the constitutional challenge is over before it begins. This conclusion is inescapable in light of one of the canonical expressions of the rational basis test: *FCC v. Beach Communications*.\(^5\) The key question was whether to uphold a regulation that distinguished “between facilities that serve separately owned and managed buildings and those that serve one or more buildings under common ownership or management.”\(^6\) The D.C. Circuit—in a short per curiam opinion, joined only by Judges Edwards and Douglas Ginsburg—found this rationale to be “a naked intuition, unsupported by conceivable facts or policies.”\(^7\) Dissenting from this pair of ideological opposites was Chief Judge Mikva, who dissented on the strength of a previous concurrence in the case\(^8\) without further elaboration. The adverse decision below did not deter Justice Thomas when he wrote for an eight-member majority of the Supreme Court, with only Justice Stevens concurring in the result:

On rational-basis review, a classification in a statute such as the Cable Act comes to us bearing a strong presumption of validity . . . . Moreover, because


\(^3\) Perhaps the most famous example can be found in *Haw. Hous. Auth. v. Midkiff*, 467 U.S. 229, 241 (1984): “Where the exercise of the eminent domain power is rationally related to a conceivable public purpose, the Court has never held a compensated taking to be proscribed by the Public Use Clause.” On this basis, the Court held that the legislature could require a landlord to sell his reversion to his tenant through the intervention of state power, which was only exercised after the tenant put the purchase price into escrow so that the government never faced any financial risk.

\(^4\) See *Nat’l Fed’n of Indep. Bus. v. Sebelius*, 132 S. Ct. 2566, 2616–17 (2012) (Ginsburg, J., dissenting) (citations omitted) (internal quotation marks omitted) (parenthetical omitted) (“This [C]ourt will certainly not substitute its judgment for that of Congress unless the relation of the subject to interstate commerce and its effect upon it are clearly non-existent.’ When appraising such legislation, we ask only (1) whether Congress had a ‘rational basis’ for concluding that the regulated activity substantially affects interstate commerce, and (2) whether there is a reasonable connection between the regulatory means selected and the asserted ends. In answering these questions, we presume the statute under review is constitutional and may strike it down only on a ‘plain showing’ that Congress acted irrationally.” (citing *Hodel v. Indiana*, 452 U.S. 314, 326 (1981))).


\(^6\) Id. at 309.

\(^7\) *Beach Commc’n’s, Inc. v. FCC*, 965 F.2d 1103, 1105 (D.C. Cir. 1992).

\(^8\) *Beach Commc’n’s, Inc. v. FCC*, 959 F.2d 975, 988–91 (D.C. Cir. 1992) (Mikva, C.J., concurring in part and concurring in the judgment).
we never require a legislature to articulate its reasons for enacting a statute, it is entirely irrelevant for constitutional purposes whether the conceived reason for the challenged distinction actually motivated the legislature.9

Most modern legislative schemes are complex with many moving parts. The rationales that can be given to support them are as numerous as they are flimsy. A decision rule that allows one good rationale to dictate the outcome provides an “open sesame” that virtually guarantees that any statute subject to the rational basis test is constitutional at birth, no matter how dubious its political or intellectual pedigree.

The simple fact that some government legislators or officials are prepared to back a particular course of action becomes proof positive that someone benefits from the statute, which is all that is needed to make this claim. It is therefore difficult to find any type of government action that is exposed to special vulnerability under the rational basis test. Both structural and individual rights challenges are cut down by the same scythe.

The question is why this should be the case on grounds of either constitutional text or constitutional structure. On the former, there is no explicit differentiation among the various guarantees that are set out in the Constitution, which otherwise might lead anyone to say that (some forms of) speech and some forms of government action should receive higher levels of scrutiny. All the commands found in the Constitution are written in the strong indicative: we know what the government can and cannot do, with no leeway for error. In each substantive area, to be sure, there are separate interpretive questions that cry out for particular solutions; but as a textual matter, the basic guides of interpretation are no different from those of other texts of either a contractual or statutory origin.

As I have argued at length elsewhere, there are at least four challenges that are presented by cryptic texts such as those found in documents from the Ten Commandments to the Constitution.10 The first of these is the textual challenge itself. We have to have a definition of the term “commerce,” and by ordinary English that term is defined in opposition to such activities as manufacture, mining and agriculture—all of which the post-New Deal jurisprudence nevertheless says is included in its definition. It is as if the Uniform Commercial Code covered agriculture, manufacturing and mining.11 Similarly, we have to give a definition to private property, which in modern constitutional discussion is often

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11. See e.g., Wickard v. Filburn, 317 U.S. 111, 118 (1942) (upholding the intrastate regulation of how much wheat a farmer could grow on his own farm even though the wheat was “not intended in any part for commerce but wholly for consumption on the farm.”).
limited to the right to exclude, without including the rights of use and disposition that have long formed part of the common understandings of the use of that term in private law. It is no mere coincidence that the first of these major changes is used to expand the scope of federal power, and the second is used to reduce the level of individual protection against that expanded government use, as embodied, for example, in the untenable constitutional distinction between a permanent physical taking (ostensibly subject to a per se rule) and a regulatory taking that is subject to the lower rational basis standard.

But why engage in these pyrotechnics in the first place? The central challenge of constitutional law is to make sure the government is strong enough to provide for peace and good order, but not so strong that it consumes or destroys the private interests it is instituted to protect. In dealing with the role of regulation, it is always wise to remember that governments suffer from two serious weaknesses. First, their knowledge base is often insecure, for it is difficult for any benevolent party at the center to understand and combine in any metric the preferences of millions of different people. The Hayekian critique of centralized power, and its insistence that market-based exchanges offer the best way to overcome various information deficits, is as powerful today as it was eighty years ago. Second, there is the danger of motivation, well captured in the concern that Madison expressed in Federalist 10. The point about these elements is that they both are all pervasive whenever and however government chooses to exert its powers, be it through legislation, regulation, administrative

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12. See Kaiser Aetna v. United States, 444 U.S. 164, 179–80 (1979) ("[W]e hold that the 'right to exclude,' so universally held to be a fundamental element of the property right, falls within this category of interests that the Government cannot take without compensation.").

13. Compare United States v. Gen. Motors Corp., 323 U.S. 373, 377–78 (1945) ("The critical terms are 'property,' 'taken' and 'just compensation.' It is conceivable that the first was used in its vulgar and untechnical sense of the physical thing with respect to which the citizen exercises rights recognized by law. On the other hand, it may have been employed in a more accurate sense to denote the group of rights inhering in the citizen's relation to the physical thing, as the right to possess, use and dispose of it. In point of fact, the construction given the phrase has been the latter.", with Penn Cent. Transp. Co. v. New York, 438 U.S. 104, 124 (1978) (describing the takings inquiry as "essentially ad hoc" and finding that "interference arising from some public program adjusting the benefits and burdens of economic life to promote the common good" did not necessarily constitute a taking even if it infringed on rights of use and disposition).

14. Loretto v. Teleprompter Manhattan CATV Corp., 458 U.S. 419, 426 (1982) (emphasis added) ("We conclude that a permanent physical occupation authorized by government is a taking without regard to the public interests that it may serve.").

15. Penn Cent. Transp. Co., 438 U.S. at 130–31 ("Appellants concede that the decisions sustaining other land-use regulations, which, like the New York City law, are reasonably related to the promotion of the general welfare, uniformly reject the proposition that diminution in property value, standing alone, can establish a 'taking' . . . .").


17. The Federalist No. 10 (James Madison) ("By a faction, I understand a number of citizens, whether amounting to a majority or minority of the whole, who are united and actuated by some common impulse of passion, or of interest, adverse to the rights of other citizens, or to the permanent and aggregate interests of the community.").
action or even judicial behavior. These dangers, for example, are every bit as great when the government engages in land use regulation as in the permanent or temporary occupation of real estate. Using high-level scrutiny in physical occupation cases and low-level scrutiny for “mere” regulation offers redress against modest intrusion to parties who are exposed to massive regulatory losses. Similarly, as the recent decisions in Amarin Pharma v. U.S. Food & Drug Administration and United States v. Caronia extensively document, and as a study of the FDA shows, regulating commercial speech can pose dangers equal to or more dangerous than regulating political speech or artistic endeavors. The upshot of this is that the rational basis test is utterly unsuited to deal with basic challenges because its adoption presupposes a level of good faith that governments often do not have.

More than abstract speculation drives the quest for more ambitious judicial review, which works in other areas where government action poses threats to economic or political competition. Note, for example, the contrast between the former examples and the tough-minded approach to the dormant commerce clause, where the movement towards strict scrutiny leads to asking the right questions. Is there an anticompetitive tilt to legislation that gives an unwarranted advantage to insiders over the outsiders? Is there some specific danger that needs to be combated in the risks that one person or firm’s activity poses to the health and safety of others? The point is that the right concerns can prevail if only one tries. The same is true with respect to speech, where magically the same formula applies: a close look at any justifications for restrictions on speech reveals that such restrictions are usually tied to the threat or use of force, or to false and misleading speech, restrictions that both have a secure place within the classical liberal framework.

It is therefore critical to develop a set of interpretive techniques that capture these structural and substantive concerns. In dealing with this issue, one has to start with the text and give the words their ordinary interpretation at the time of the constitutional adoption. But textualism in this sense is only a necessary, never a sufficient, condition for the interpretation of the Constitution, or indeed any other document. The correct modes of interpretation dovetail neatly with the problem of incomplete knowledge and factional intrigue. As to the first, few

18. See, e.g., Stop the Beach Renourishment, Inc. v. Fla. Dep’t of Envtl. Prot., 560 U.S. 702, 711 (2010) (“The petitioner here, Stop the Beach Renourishment, Inc., is a nonprofit corporation formed by people who own beachfront property bordering the project area . . . .”).
20. 703 F.3d 149 (2d Cir. 2012), discussed infra text accompanying note 70.
22. See, e.g., Dean Milk Co. v. Madison, 340 U.S. 349, 354 (1951) (holding that a state cannot discriminate against interstate commerce “even in the exercise of its unquestioned power to protect the health and safety of its people, if reasonable nondiscriminatory alternatives, adequate to conserve legitimate local interests, are available.”).
texts can anticipate all the government actions that may be challenged. Some degree of adaption is necessary to deal with a wide range of circumstances that have no explicit textual warrant. This incompleteness of all basic texts is well known to the parties, be they public or private, who are bound by them. It follows therefore that some fraction of them at least will do whatever they can to avoid their application. Clearly, the risk of incompleteness and circumvention offers a challenge to any system of constitutional interpretation; and legal norms, conventions, and rules have to be devised to stop that from happening. Such rules are constantly applied against private parties. For example, the prohibition against killing covers not only the direct application of force, but similar cases, most notably setting poison before an unsuspecting person. But Congress, like private parties, is often eager to circumvent limitations on its power as well. If Congress cannot directly regulate the use of child labor in domestic production, then it will impose a prohibition on those sales in interstate commerce by firms that use child labor. And if the prohibition is struck down, Congress will then replace it with a somewhat less efficient tax intended to perform the same function. If property is protected against taking, then Congress will just flood someone else’s land without bothering to take title. In all these cases, the law has to develop doctrines to protect against subversion of the basic guarantee, which the anti-circumvention rules have to cover, on both structural and individual rights issues.

Next, constitutional interpretation follows the private law insofar as it allows for justifications for prima facie wrongs. For example, deliberate force may be used in self-defense, even if excessive force may not. And so it is that governments can indeed exclude some goods from within their boundaries in order to preserve local flora and fauna. And it is possible to take property (even literally and physically) in order to disarm a potential thief or to prevent the occurrence of a nuisance. This is why a key non-textual element of modern constitutional interpretation—the police power—is added in as a qualification to every jurisdictional element and substantive guarantee. But as with the private law, it is necessary that these be limited in their scope so that the essential constitutional guarantee is not eviscerated by recognizing necessary exceptions to it. Thus it is legitimate for the government to stop the creation of a common

23. See, e.g., Dig. 9.2.7.6 (distinguishing between occiderit, i.e., killing, and mortis causam praestit-erit, i.e., furnishing a cause of death; the former being textual, the latter creating liability by way of extension).
28. Note that the so-called per se rule for physical takings in Loretto v. Teleprompter Manhattan CATV Corp., 458 U.S. 419 (1982), is a serious misnomer. There are many justifications for seizing physical property without compensation, including for misbranded and adulterated drugs. The point here is that the justifications need to be individually set out and justified. The same approach should apply to regulatory takings as well.
law nuisance, but not economic competition—at least so long as the common law rules were followed before stopping competition (as opposed to stopping monopoly) became a legitimate government function.29

Working out these details is the ultimate non-textual enterprise, for it depends on the larger substantive theory of rights that is embedded in the Constitution, which on these points is a distinctively classical liberal doctrine, with its strong protection of private property, traditionally understood as the guardian of every other right, religion, speech, and contract.30 In dealing with these issues, the appropriate mode of transformation asks this one simple question: Could one private party protest the actions of another and do so in a way that commands legal relief? If the answer to that question is yes, then a police power justification is available. But if the answer to that question is no, then there is no police power justification, and the matter quickly turns to the issue of just compensation, which could be either in cash or in kind, with the former being more common when the burden of the regulation hits disproportionately on a single person and with the latter being appropriate for widespread regulations that harm and benefit many individuals simultaneously.

Finally, it is necessary to select the correct remedy against a constitutional violation, just as if it were the commission of a tort or a breach of contract. The issues here are difficult. The basic choice is between injunctive relief and damages. But that is only the tip of the iceberg. Injunctions may be complete or partial, temporary or permanent, conditional or absolute, reviewable or not. Likewise, damages could be temporary or permanent; and they could respond to the protection of either a restitution, reliance, or expectation measure of damages, just as in private law. The point of this exercise is to identify the necessary and common complexities in constitutional law, which mirror the similar interpretive challenges in common law disputes between private persons. If anything, constitutional law has an additional layer of difficulty because it has to take into account not only private rights but also the elaborate institutional structures by which public rights and duties are defined and enforced.

No interpretive system can avoid these difficulties. But just because that is also true in this context does not call for articulating some “living constitution.”31 The matters of nuisance and self-defense, for example, come from a general theory of rights, which was as relevant to ancient and medieval times as it is to the present. Indeed, all these were in fact addressed in dealing with these matters. None of the concerns here relate to the vagaries of legislative history, whether by committee reports (for which there is some credibility) or strategic

31. For that approach, see generally Jack Balkin, Living Originalism (2011).
statements by individual legislators (that usually should be greeted with a great deal of skepticism).

The question then arises, where in this complex structure is there any room at all for the rational basis test? The correct answer, I believe, comes in two parts. The first is that it does not have any role to play in connection with any effort of the government to regulate the behavior of private parties. I mean this in two senses, given the enormous expansion of the use of conditional approvals or exactions (which do have a role, for instance, in the area of drug regulations when the government issues its positions on such matters). The key point to understand here is that the use of conditional permits is quite different from actions by the government to manage its own affairs, as it does whenever it engages in the standard functions necessary to operate a night watchman state on the one hand or in carrying out the expanded duties that arise in connection with the post-New Deal state on the other. Clearly the problems are amplified with the vastly expanded role of government as an employer or owner, but the basic principles remain the same in both instances. When the government manages its own affairs, it will, like any private firm, make errors a fair number of times. It could not continue to operate under a regime that simultaneously requires it to compensate the victims of its errors whenever it is wrong but also does not allow it to capture some substantial fraction of the social gains from its private beneficiaries when it turns out to be right.

The explanation is simple, given the asymmetrical returns under any regime of strict tort liability. In general, we think that well-disposed government officials will produce, on net, benefits for the country at large—otherwise we would not ask them to engage in certain functions. At this point, it would create grotesque incentives if government agents had to internalize all the costs but were unable to internalize the benefit. It is a dangerous business to treat positive social actions as net negatives on matters of liability. For example, it is highly inadvisable to hold people who attempt rescues liable for the harms that they are unable to prevent, and even for the harms that they cause, when the rescue action offered expected \textit{ex ante} value. The famous early case that illustrates this danger is the \textit{Tithe Case},\textsuperscript{32} where the defendant moved the plaintiff’s grain from the fields, where it was certain to be destroyed, to a safer location in a barn, where it was destroyed for causes not specified in the opinion. \textit{Ex post}, the plaintiff receives insurance; but, from the \textit{ex ante} perspective, a rule that holds a rescuer responsible for the losses, while offering that party nothing for the gains, will kill the market in assistance. Who will perform such needed tasks when private incentives diverge from public welfare? A privilege is therefore necessary in these cases.

Closer to hand is the development of a complex law of sovereign and official immunity.\textsuperscript{33} Considerations like this lead to the creation of absolute immunity

\begin{footnotesize}
\begin{enumerate}
\item[32.] Y.B. Trin., 21 Hen. 7, f. 26, 27, 28, pl. 5 (1506).
\item[33.] \textit{See, e.g.}, The Federal Tort Claims Act, 28 U.S.C. § 1346(b) (2016).
\end{enumerate}
\end{footnotesize}
for judges and public prosecutors, while still allowing for the imposition of other types of sanctions in the event of serious error. The basic point is that so long as there is a perceived necessity of public service, the misalignment of incentives works no better than it does in private necessity cases where individuals who in times of necessity intervene to help others are later tagged with the loss.\footnote{34} It is for just this reason that managers get the benefit of the business judgment rule in ways that regulators should not. The government always needs a more powerful justification for the use or threat of force against unwilling individuals.

Yet at the same time, it is imperative to recognize that the acceptance of a good faith standard, as under the business judgment rule, is a far cry from the rational basis standard as announced in the canonical Supreme Court cases. One of the requirements of good faith is that the speaker means what he says and says what he means. It is utterly incompatible with the notion of good faith that the government can change its story when it defends its position in court, as it is allowed to do in rational basis cases. No corporate or government official could do that without facing serious charges of gross impropriety. The very fact that the rational basis test has no known equivalent in the standards dealing with fiduciary or individual responsibility shows just how far the law has strayed from well-established historical principles. The switch, moreover, is not inconsequential, as rational basis review pervades our current legal regime. In particular, this tension is often present in FDA cases. In these cases, the government is not acting as the physician of ordinary citizens, which it does, for instance, when it provides health care to its employees such as military personnel. Rather, in cases involving the FDA (or most any administrative agency), it acts as a regulator who interferes at will with physician-patient relationships on the ground that it has a better understanding of the risks and benefits of any drug that it chooses to keep off the market. It is important to see how this plays out, and it is not a pretty picture.

In the remainder of this article, I shall look at the overall pattern of development. Part I offers a capsule summary of the history of FDA regulation. Part II explores this in three sections. The first explores the rise of the rational basis test for drug approval. The second speaks about the off-label exception to the FDA approval process. The third asks about the First Amendment override of the FDA on the publication of truthful information for unapproved drugs. All of these intersecting issues raise questions about the scope of the police power justifications for government regulation. Part III deals with one seemingly obscure, but vital, question: the proper FDA treatment of compound drugs, particularly with respect to the removal of drugs from the market. In looking over these materials, it is never quite clear whether the problem is best under-

stood as one to which the rational basis test is inapplicable, or one to which it is applicable but is nonetheless misapplied. In these cases, the standard of review clearly comes into play because the higher standard in speech cases has led the government to suffer some stinging defeats. In this context, a close-up look at how the rational basis test works offers powerful confirmation that it should never—repeat never—be used as the litmus test in evaluating coercive government action.

I. THE EVOLUTION OF FDA AUTHORITY

The first major step in drug regulation was the passage of the Federal Food and Drug Act of 1906,35 enacted in light of growing concerns over contaminated food and quack drugs. The law was intended to stop the proliferation of fraud in the provision of drugs through its prohibitions of adulteration and misbranding.36 Owing to the strong commerce clause limitation found in United States v. E.C. Knight Co.,37 the 1906 Act allowed the government to regulate the manufacture of drugs only in the territories.38 Other drugs could only be regulated insofar as they were shipped or transported in interstate commerce,39 which led to the emergence of a complex jurisdiction that asked when a particular drug, whether isolated or blended, entered or left commerce, a matter still important today.40 Given its limited objectives and strong fraud-prevention

36. Id. at §§ 7 (adulterations), 8 (misbrandings).
37. 156 U.S. 1, 13 (1895) ("The regulation of commerce applies to the subjects of commerce, and not to matters of internal police. Contracts to buy, sell, or exchange goods to be transported among the several states, the transportation and its instrumentalities, and articles bought, sold, or exchanged for the purposes of such transit among the states, or put in the way of transit, may be regulated; but this is because they form part of interstate trade or commerce. The fact that an article is manufactured for export to another state does not of itself make it an article of interstate commerce, and the intent of the manufacturer does not determine the time when the article or product passes from the control of the state and belongs to commerce.").
38. Supra note 35, at § 1 ("Sec. 1. MANUFACTURE OF ADULTERATED FOODS OR DRUGS. That it shall be unlawful for any person to manufacture within any Territory or the District of Columbia any article of food or drug which is adulterated or misbranded, within the meaning of this Act.").
39. Supra note 35, at § 2 ("SEC. 2. INTERSTATE COMMERCE OF ADULTERATED GOODS. That the introduction into any State or Territory or the District of Columbia from any other State or Territory or the District of Columbia, or from any foreign country, or shipment to any foreign country of any article of food or drugs which is adulterated or misbranded, within the meaning of this Act, is hereby prohibited.").
40. See United States v. Regenerative Sciences, LLC, 741 F.3d 1314, 1320 (D.C. Cir. 2014) ("Equally untenable is appellants' contention that because the Procedure occurs entirely within the state of Colorado, the Mixture lacks a sufficient connection to interstate commerce to permit federal regulation under the Commerce Clause. It is simply impossible to square this argument with the last seventy years of Commerce Clause jurisprudence . . ."); United States v. 40 Cases, More or Less, 289 F.2d 343, 344 (2d Cir. 1961) ("The single question before us on this appeal is whether § 304(a) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 334(a), authorizes the United States to proceed against and seize mislabeled or adulterated cans of blended vegetable oils mixed entirely within the State of New York from various oils shipped under proper labels from other states and foreign countries.").
rationale, the 1906 Act falls comfortably within the narrow scope of the police power of the time.

The first major expansion of the basic act took place in 1938, right after the expansion of federal commerce clause power. The government received the added power to regulate the manufacture of drugs within the states and to test them not only for purity—which is the basic fraud question—but also for safety. This major extension raises serious implementation problems for the simple reason that drugs are not simply safe or not safe. All drugs promise a spectrum of risks and benefits, and the central task is to decide how to weigh the one against the other, both in individual cases and in the aggregate. At this point, the government power goes beyond the libertarian function of stopping the production of fraud, inasmuch as the government, in principle, is allowed to substitute its judgment about whether some drug is safe enough in place of the judgment of patients and their physicians.

This judgment came to be known as GRAS—the “generally recognized as safe” standard—which dominated much of the FDA law after 1938 and before 1962. In this period, the government’s power of review was sharply limited. Private applicants had to submit their application for new drugs to the government, and those applications were deemed approved if the government did not demand further information about their use within a narrow window of approximately sixty days. By this time, the pharmaceutical industry had developed systematic research protocols such that, as noted by Justice Douglas in Weinberger v. Hynson, Westcott & Dunning, Inc., “[b]etween 1938 and 1962 FDA had permitted 9,457 NDA’s [New Drug Applications] to become effective. Of these, some 4,000 were still on the market.”

In addition, so-called me-too variations of these pioneer drugs could be introduced into the market without any form of prior approval on the ground that they did not materially differ from the initial, usually patented, drug they imitated. The FDA also issued advisory opinions to companies that their products were generally recognized as safe by experts within the field. The change in the legal system did not make a dent in the patterns of investigation or licensing.

Yet all that changed after the thalidomide episode of 1961 which resulted in the passage of the Kefauver Harris Act of 1962, which the FDA continues to hail for “the scientific safeguards used today by the Food and Drug Administration (FDA) to ensure that consumers will not be the victims of unsafe and ineffective medications,” without any awareness of the flip side of the coin—unnecessary delay and government error. The thalidomide incident clearly constituted a safety issue, for which it is clear that once that defect became known, no one would wish to take the drug during the first trimester of

42. Id.
pregnancy. The response to that incident was to transform the FDA into the powerful agency that it is today. There were two key steps. First, all drugs were required to go through some preclearance treatment with elaborate submissions and exhaustive clinical tests, which one recent estimate placed at $2.6 billion for a new clinical entity, with close to half those costs attributable to the time-cost of money driven by the long period for clinical trials. Second, testing of drugs was not only for safety, but also for effectiveness, so that GRAS became GRASE, or “generally recognized as safe and effective.” The reforms raised huge questions: how should drug approval take place, and, critically, what should be done with drugs that had been approved under the 1938 standard in the post-1962 period? It is at this point that the role of the rational basis test kicked in.

II. CHEVRON BEFORE CHEVRON

A. The Rise of the Rational Basis Test

Within the new statutory framework, the key response was the powerful judicial conviction that deference to the administrative agency should apply on matters of public health. “Constitutional rights of privacy and personal liberty do not give individuals the right to obtain laetrile free of the lawful exercise of government police power.” This substantive position on the expansive reading of the police power—a Chevron-like deference before Chevron—was echoed when, in United States v. Rutherford, the Supreme Court held that expert agencies were entitled to substantial deference. Thus, the dominant legal trope given to Congress made it easy for Justice Marshall to conclude (correctly) that Laetrile was a new drug on both the 1938 and 1962 Acts, and that the statutory language “makes no special provision for drugs used to treat terminally ill patients,” no matter how desperate their condition, so that the various plaintiffs and their spouses were out of luck.

45. It should be noted that thalidomide is now on the market as a treatment for multiple myeloma, but obviously it is not on the market for pregnant women. For a recent account, see Natalie Zarrelli, How Thalidomide Went from Medical Disaster to Miraculous Cancer Treatment, ATLAS OBSCURA (Jan. 18, 2016), http://www.atlasobscura.com/articles/how-thalidomide-went-from-medical-disaster-to-miraculous-cancer-treatment.


47. Carnohan v. United States, 616 F.2d 1120, 1122 (9th Cir. 1980).


49. Id. at 553–54 (citations omitted) (“As this Court has often recognized, the construction of a statute by those charged with its administration is entitled to substantial deference. Such deference is particularly appropriate where, as here, an agency’s interpretation involves issues of considerable public controversy, and Congress has not acted to correct any misperception of its statutory objectives.”).

50. Id. at 551.
Weinberger and Rutherford were key judicial decisions that backstopped the decision of Judge Thomas Griffith in Abigail Alliance for Better Access to Developmental Drugs v. von Eschenbach.\textsuperscript{51} Abigail Alliance rebuffed the claim that all individuals are entitled on constitutional grounds to have access to experimental drugs that have passed a Phase I trial, which is designed to measure responsiveness to high dosages that could have serious side effects. By this time, the assertion of police power interests had been strengthened by the Supreme Court decisions in Washington v. Glucksberg\textsuperscript{52} and Vacco v. Quill,\textsuperscript{53} which rejected constitutional claims regarding the benefits of euthanasia/assisted suicide. The applicable test used in both those cases asked whether that right was “deeply rooted in this Nation’s history and tradition,” which, given the extensive history of regulation of health and safety, was a most difficult claim to defend on those grounds.

The most obvious difference between Glucksberg and Vacco on the one side, and Abigail Alliance on the other, is that in the former the plaintiffs wanted to end their lives, while in the latter, they were intent on saving them. It is easier to see abuse by family members and hospitals in the former situation. Indeed, I think that the concern is so strong that the Court was right to reject the unvarnished claim to the right of assisted suicide, given the need to fashion serious safeguards against its abuse.\textsuperscript{54} Yet, the carryover to the class of cases in which patients seek treatment or cures is difficult at best. First, the police power, even with deference, does not give either the state or federal government the power to take away all health care decisions from the individual. No matter what the history might have been, no one would countenance a decision that the government could use its power of health and safety to force people to take prescribed medicines that have survived exhaustive FDA scrutiny in the treatment of particular diseases, or to eat those foods and follow those diets that promise to improve health and longevity.\textsuperscript{55} In those cases, right now it is utterly immaterial that expert administrators, acting in good faith, have issued the relevant decrees. The intrusion on personal liberty with that nonstop activity would be attacked on substantive grounds. It would be merely a matter of detail to find that clause on which the argument opposing such intrusion could be based, but substantive due process would be an obvious candidate for that development, given that it is the ostensible basis for the right (given, at least, the absence of any coherent jurisprudence that defines the privileges or immunities of the citizens of the United States). Indeed, the issue would never get to that

\begin{itemize}
    \item \textsuperscript{51} 495 F.3d 695 (D.C. Cir. 2007).
    \item \textsuperscript{52} 521 U.S. 702 (1997).
    \item \textsuperscript{53} 521 U.S. 793 (1997).
    \item \textsuperscript{54} For discussion on this point, see Richard A. Epstein, Mortal Peril: Our Inalienable Right to Health Care? 329–43 (1997), written before Glucksberg and Vacco.
    \item \textsuperscript{55} Cf Nat’l Fed’n of Indep. Bus. v. Sebelius, 132 S. Ct. 2566, 2588 (2012) (“[M]any Americans do not eat a balanced diet . . . Under the Government’s theory, Congress could address the diet problem by ordering everyone to buy vegetables.”).\end{itemize}
point because even the statist traditions that dominate the health care area are not strong enough to overcome that bedrock assumption. It is also instructive to note that the claim here would not be in any way tied to the terminal condition of the applicants. Healthy people cannot be made duty bound to take medicine or to eat broccoli.

The question then arises as to why the argument should be different when these same people insist on gaining access to drugs that these same government officials regard as unsafe for personal consumption and use. It is worth noting that if any private person sought to block another’s access to drugs, the conduct would amount to intentional interference with advantageous relations, a tort that has been established for centuries.\(^{56}\) The FDA uses the government to supply its guns to keep patients from the care of their physicians, and the deterrent effect of this backing is so potent that it is never used. In this regard, the tort is analogous to defamation, which involves the disruption of voluntary arrangements by misrepresentation, a more frequent but less effective way to disrupt behaviors.\(^{57}\)

So, by this view, the question is, normatively, what ground does the government have for taking aggressive actions on paternalist grounds, actions that would never be tolerated if committed by any private individual? It is one thing to protect individuals by broad rules against false expectations peddled by con artists. But on this critical point, the difference between \textit{Rutherford} and \textit{Abigail Alliance} is quite different. The Alliance was formed by Abigail’s father, Frank Burroughs, because the late Abigail Burroughs was subject to prolonged denials of the use of the drug Erbitux, then in clinical trial.\(^{58}\) She could not participate in a clinical trial since she had head and neck cancer, not colon cancer, and she was unable to obtain a compassionate exemption from drugs that had not reached the general market. But in her case, the treatment was recommended by her physicians at Johns Hopkins University, with respect to a drug that is now in common use with FDA approval.

The central point is this: it is a mystery why her choice to use a particular drug should be regarded as a public health issue or even a matter of economic liberty, i.e., the right to enter some occupation or business without government restriction. It looks to be a personal health issue in which her decision about whether to take the drug can be made independently of that decision made by

\(^{56}\) See, e.g., \textit{Keeble v. Hickeringill}, 103 Eng. Rep. 1127, 1128 (K.B. 1707) ("One schoolmaster sets up a new school to the damage of an ancient school, and thereby the scholars are lured from the old school to come to his new. (The action was held there not to lie.) But suppose Mr. Hickeringill should lie in the way with his guns, and fright the boys from going to school, and their parents would not let them go thither; sure the schoolmaster might have an action for the loss of his scholars."); \textit{see also Tarleton v. McGawley}, 170 Eng. Rep. 153 (K.B. 1793).

\(^{57}\) \textit{See Restatement (Second) of Torts} \S 559 (1977) ("A communication is defamatory if it tends so to harm the reputation of another as to lower him in the estimation of the community or to deter third persons from associating or dealing with him.").

\(^{58}\) \textit{Abigail Alliance, Our Story}, \url{http://www.abigail-alliance.org/story.php} (last visited Aug. 8, 2016).
anyone else. Given the private institutional safeguards already in place, is it appropriate to let the cumbersome machinery of the FDA, run by people who have no knowledge of her personal condition, hold complete veto power over her choice? In this instance, her cells exhibited a trait that, in the opinion of her physicians, made her an ideal candidate for the drug.

The issue was one on which the FDA delayed unnecessarily because its medical experts did not think that the evidence from clinical trials was strong enough to guarantee the safety of the various potential drugs. But that position will always be true for drugs that are intended to treat rare, and often fatal, conditions. Consider alternative approaches the FDA might have taken. There was some respectable, albeit anecdotal, evidence that boys who took these medicines continued to lead active lives, while those without the medicine were confined to wheelchairs before they died. There was a large network of pediatric neurologists who supported the continued use of the drugs. And there was, as there always is with children’s diseases, an active and engaged parent network whose members probably know more about the condition and its possible treatment than the FDA experts, precisely because these parents talk and listen to their children’s physicians.

Finally, on September 19, 2016, the FDA granted accelerated approval to Exondys 51 (eteplirsen), with the caveat that further clinical trials would need to be conducted. The FDA release did not mention that Dr. Janet Woodcock, M.D., director of the FDA’s Center for Drug Evaluation and Research, had to fight internal opposition from senior FDA officials who claimed that her decision would “lower agency standards.” There is not the slightest evidence that the FDA physicians who lobbied against the drug knew the first thing about expected value calculations.

The Woodcock decision represents its own profile in courage. But it is important to recognize that, however welcome the move, it is also seriously incomplete. A second drug, Kyndrisa (drisapersen), was left untouched by the


61. See John Carroll, Senior FDA Officials Warned that Approving $300,000 Duchenne Drug Will Lower Agency Standards, ENDPOINTS NEWS (Sept. 19, 2016), https://endpts.com/senior-fda-officials-warned-that-eteplirsen-ok-would-lower-fda-standards/ (“The acting chief scientist at the agency, Luciana Borio, argued that an approval would lower the agency’s standards and encourage other developers to pursue the same kind of lobbying campaigns employed at Sarepta. And she accused Sarepta of acting irresponsibly by knowingly pushing ‘misleading’ information about the drug. Ellis Unger, director of the office of drug evaluation, scoffed at the data Sarepta offered, calling the drug a ‘scientifically elegant placebo.’”).
Woodcock approval, which gives the sellers of Exondys 51 a huge competitive advantage that is not warranted by any medical evidence. Indeed, it should be painfully clear that the insistence of large-scale clinical trial has a huge anticompetitive effect when the pool of potential participants has to be divided among two or more rival entrants. The FDA policy should adapt to this constraint and allow both drugs onto the market so that the patients, physicians, and parents can be in a position to adopt differential strategies. One can only speculate how many other drug treatments never get developed at all because potential firms and their investors cannot see a clear path to market given the likely FDA intransigence regarding approval.

There is a larger lesson here. No one should ever belittle the difficulties and side effects that emerge during clinical trials, but as a matter of first principle the issue should never be whether the FDA has made the correct risk assessment. The threshold question should be, once the information from trials is gathered, organized and published, whether the FDA should substitute its judgment for patients, their families, and their physicians. On this score, the expert FDA committees should surely have their say, although their selection criteria that tend to exclude physicians that work for branded companies can skew their collective judgment. But I see no reason why parents cannot make the choice on whether to use that drug on their child, even if it provides no benefit for anyone else. Yet time and time again, access delays can prove fatal for unapproved drugs. Sadly, however, the FDA cannot formulate a coherent standard for deciding what drugs to approve and when. Its insistence on statistical significance through clinical trials creates long delays and deters many promising lines of treatment long before a final decision must be made. To be sure, once approved, the expected treatment value of a drug is likely to be positive, but it hardly follows that the expected value is negative prior to that approval. If it is said that patients and their doctors cannot be trusted to make decisions about unapproved drugs in tandem, why then let them navigate the myriad treatment options once these drugs are approved? And would it be constitutional to require that each and every course of chemotherapy or drug treatment, in the name of public health, must go through an FDA preclearance response?

Unfortunately, nothing in Abigail’s Alliance, or any of its companion decisions, asks the right questions about patient choice. It is quite one thing to protect traditional liberties. It is quite another to extol traditional forms of government regulation, many of which were dysfunctional from the time they were put in place precisely because many cut far deeper than the traditional state police power over force and fraud. Just ask this simple question: what

would happen if the FDA were unable to block the use of any drug that passed Phase I clinical trials? Would the world be worse or better off? The answer is better off, because the absence of government action would speed the rise of, and expand the scope of, voluntary intermediaries that deal with the information gaps of patients and physicians in deciding between new and old treatments. That is why organizations such as the National Comprehensive Cancer Network (NCCN) thrive even with the FDA in place, as they do a better job getting information to physicians in a timely fashion about which drugs to use, in what sequence, in what dosages, and in what combinations. That is why the NCCN and similar organizations survive in the first place.\textsuperscript{63} In fact, these organizations do such a good job that the FDA warnings are widely disregarded precisely because other information sources are better.\textsuperscript{64} Fortunately, the government has no monopoly over information, which is why the information market works better than the market on actual release.\textsuperscript{65} Here is a case where there is no rational basis to prefer confused public health and police power rationales to the question of individual choice. Individuals should not be forced to beg the government for permission to take the only options that offer them some kind of relief.

B. Off-Label Uses

The issue with FDA competence comes to a head in connection with off-label uses, i.e., the use of approved drugs by physicians for conditions for which the FDA has not approved them. A physician’s ability to make off-label uses is almost an historical afterthought, which is said to follow from the observation that individual physicians who make off-label uses in their own practice are not caught by the misbranding prohibition.\textsuperscript{66} The enormity of this exception means that physicians can use any approved drug that they want to treat any condition, no matter what the FDA says or does. It is equally clear that the exception is the lifeblood of modern American medicine, especially in cancer cases, where drugs are routinely used in a high percentage of cases, without any of the formal


\textsuperscript{64.} See Richard A. Epstein, Against Permititis, 94 Minn. L. Rev. 1, 25–30 (2009) (detailing the advantages of warnings by voluntary associations relative to FDA warnings).

\textsuperscript{65.} On this topic I put aside the possibility of tort liability for warnings that are in compliance with the FDA standards, which is a confused subject, to say the least. Compare Wyeth v. Levine, 555 U.S. 555 (2009) (denying federal preemption), with Pliva, Inc. v. Mensing, 564 U.S. 604 (2011) (finding federal preemption). For standardized upstream risks, safe harbors are essential. It is one on which the FDA has equivocated.

\textsuperscript{66.} See United States v. Evers, 643 F.2d 1043, 1048 (5th Cir. 1981) (“[T]he FDA has at no point contended, and the government does not argue on appeal, that the misbranding provisions of the Act prohibit a doctor from prescribing a lawful drug for a purpose for which the drug has not been approved by the FDA. To the contrary, the FDA has explicitly informed Dr. Evers that he could legally prescribe chelating drugs for the treatment of circulatory disorders.”).
clinical trials that the FDA deems necessary to put a drug on the market. The fair question to ask is whether this common practice of off-label uses somehow compromises the level of medical care provided. By the FDA protocols, the entire medical profession relies on worthless evidence. Yet, ironically, it is generally agreed that standard off-label uses set the level of customary care in medical malpractice cases and are routinely reimbursed by various insurance programs, albeit on non-uniform standards. So the question thus remains, why is it sensible to allow for any use of an approved drug, but no use, save in infrequent experimental cases, for the first use of a new drug subject to endless FDA hurdles? It should be clear that two totally different methodologies are at work. Clinical medicine does not proceed, and never has proceeded, by double-blind clinical trials in its day-to-day, and so the question is whether the FDA should be able to choke off new products by making clinical trials—which no one wishes to ban—the only game in town. The answer to that question is no, and one can only imagine the outcry if the FDA or anyone else sought to ban off-label uses of drugs lawfully on the market. The same should apply to initial uses of drugs already vetted through an initial round of safety preclearance.

C. First Amendment Protection for Publication of Truthful Information

The question of off-label use raises not only issues of licensing approval, but also issues regarding the dissemination of information to the trade and the

67. See, e.g., Monika K. Krzyzanowska, Off-Label Use of Cancer Drugs: A Benchmark Is Established, 31 J. CLINICAL ONCOLOGY 1125 (2013), available at http://jco.ascopubs.org/content/31/9/1125.full, which contains a thoughtful analysis of the pros and cons of these uses. On the issue of frequency of use, she refers to one study that found that approximately 70% of claims were on label. Among the 30% of claims considered to be off label on the basis of the FDA-approved indication, 14% conformed to National Comprehensive Cancer Network (NCCN)-supported off-label indications, and 10% of off-label use was in the same cancer site but not the stage or line of therapy as that stated on the FDA label. The annual cost of off-label use was approximately $4.5 billion. The prevalence of off-label use varied significantly by drug; agents such as bortezomib and trastuzumab were generally used on label, whereas other drugs, especially rituximab, gemcitabine, and bevacizumab, were more commonly used off than on label. In fact, off-label use of bevacizumab was the single largest contributor to the cost of off-label prescribing. See also Randall S. Stafford, Regulating Off-Label Drug Use: Rethinking the Role of the FDA, 358 NEW ENG. J. MED. 1427, 1427 (2008) (finding that approximately 21% of prescriptions were for off-label purposes).


69. One common objection to off-label use is that it disrupts the operation of clinical trials. See Final Guidance on Industry-Supported Scientific and Educational Activities, 62 Fed. Reg. 64,074, 64,080 (Dec. 3, 1997) (“FDA’s guidance also serves to protect the public health by preserving the integrity of the premarket approval process . . .”). But the ban applies even for individuals like Abigail Burroughs who are unable to participate in these trials, as well as to individuals who prefer to forgo clinical trials in order to pursue other avenues. Nor is it clear that clinical trials would not be better designed if their sponsors faced market competition.
public about such drugs’ availability and use. In line with my general libertarian inclinations, any rule that prevents the publication of truthful information should be struck down under the First Amendment unless some specific justification for it—the control of military or trade secrets, for example—can be found. No one could say that it was impermissible for physicians, economists, law professors, or anyone else to publish a critique that savages the FDA for its inhumane practices or that extols the virtues of an unapproved drug. The question then arises as to whether the FDA can prevent the company that makes a particular product from engaging in truthful publication about the drug or about the FDA’s treatment of their applications. The FDA view—namely, that these publications can be proscribed on the ground that they count as an illicit and unauthorized promotion of the drug—has run into fierce resistance as of late, most notably in two decisions that illustrate the importance of the constitutional gulf between rational basis and any higher standard of review. In United States v. Caronia, the Second Circuit, by a divided vote, held that the FDA could not bring criminal prosecutions for misbranding when Orphan Drug Company, which manufactured the drug Xyrem, hired Caronia to promote that drug through the dissemination of truthful information. The upshot of a long and convoluted argument was, yes, the speech was protected by the First Amendment, so much so that the FDA could not use that information as evidence of either some unlawful action or mental state needed to sustain its statutory claim for misbranding. The consequence of this decision was that a broader market was exposed to the drug, such that the FDA’s reduced control over its information flow was likely to lead to more off-label uses and hence higher sales. Clearly, no other party has as much incentive to push Xyrem as Orphan, so the decision represents a key way to undercut monopoly control over the drug use.

Caronia in turn set the stage for the more recent case of Amarin Pharma, Inc. v. FDA, which is discussed in greater detail because of its close examination into the FDA’s laborious approval process. Amarin had developed the drug Vascepa, for which it received FDA approval for use in lowering triglyceride concentrations over 500 mg/dL of blood—levels that expose patients to increased risks of pancreatitis and cardiovascular disease. At stake in the case was whether Amarin should be able to piggyback on its earlier work in order to address lower, but still elevated triglyceride concentrations (namely, concentrations between 200 and 499 mg/dL) for people who are already on statins. Clearly there is no sharp clinical line between these two cases, which is precisely what makes off-label uses attractive, especially when such off-label

71. See, e.g., Va. State Bd. of Pharmacy v. Va. Citizens Consumer Council, Inc., 425 U.S. 748, 761–62 (1976) (“No one would contend that our pharmacist may be prevented from being heard on the subject of whether, in general, pharmaceutical prices should be regulated, or their advertisement forbidden.”).
72. 703 F.3d 149 (2d Cir. 2012).
uses entail lower dosages with fewer side effects. It is likely, but not certain, that both the risks and benefits are lower for this second class of cases, but by the same token the net benefit could be as large, or perhaps larger, than Vascepa’s use on a more limited population at a higher dosage.

Mindful of these considerations, the FDA entered into a so-called “special protocol assessment” (SPA) with Amarin, which allowed it to do expedited clinical trials at lower levels on Vascepa. That SPA permitted the FDA to rescind the original understanding on a showing that “a substantial scientific issue essential to determining the safety or effectiveness of the drug has been identified after the testing has begun.”74 The FDA asserted such a reason after clinical trials on similar drugs had failed to establish a reduction in cardiovascular risk for patients. Indeed, an advisory committee had voted nine to two to suspend the SPA because of its doubts about the benefit side of the equation. The issue before Judge Paul Engelmayer was not whether the government had acted in breach of contract, where the FDA would have had solid defenses. Instead, the issue was with a request from Amarin, as well as certain doctor-plaintiffs, who made an “as-applied First Amendment challenge to FDA regulations that prohibit Amarin ‘from making completely truthful and non-misleading statements about its product to sophisticated healthcare professionals,’ including the doctor plaintiffs.”75

Amarin’s point was to present truthful evidence about the lower levels of triglycerides obtained and to distribute clinical studies bearing on that question that would let individual physicians decide whether that benefit was offset by conflicting evidence on the expected therapeutic effect. In response, the FDA wanted to condition these disclosures on the willingness to include FDA’s own statements stressing the limitations on the existing studies, and to block distribution of the complete record of the clinical studies. At this point, Judge Engelmayer applied the four-part Central Hudson test,76 and it was a relatively simple matter to conclude that the restrictions on speech were serious, and could not be justified given the legitimate status of off-label uses.77

The plaintiff’s case in Amarin was examined under a commercial speech rubric, which does not quite fit the publication of research data from clinical

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75. 119 F. Supp. 3d at 212.
76. Cent. Hudson Gas & Elec. Corp. v. Pub. Serv. Comm’n of N.Y., 447 U.S. 557, 566 (1980) (“In commercial speech cases, then, a four-part analysis has developed. At the outset, we must determine whether the expression is protected by the First Amendment. For commercial speech to come within that provision, it at least must concern lawful activity and not be misleading. Next, we ask whether the asserted governmental interest is substantial. If both inquiries yield positive answers, we must determine whether the regulation directly advances the governmental interest asserted, and whether it is not more extensive than is necessary to serve that interest.”).
77. Amarin Pharma, Inc., 119 F. Supp. 3d at 226 (holding that “insofar as Amarin seeks preliminary relief recognizing its First Amendment right to be free from a misbranding action based on truthful speech promoting the off-label use of an FDA-approved drug, Amarin has established a substantial likelihood of success on the merits on this point.”).
trials. Indeed, one reason to be leery of the Supreme Court approach is that the line drawing problems in this area are quite acute. A simpler approach is that, consistent with the basic libertarian thrust, the typical strict scrutiny standard applicable to typical First Amendment cases should be satisfied to justify prohibiting the dissemination of lawful information. The point here again does not go to the soundness of Amarin’s interpretation of the data. The FDA could well have been correct that the expanded use of Vascepa is unwarranted, and the FDA could express that view in its own publications targeted to these same doctors without compelling Amarin to communicate its views.

More to the point is to ask whether this same libertarian analysis makes it more difficult to keep in place the sharp difference between speech and conduct. If physicians are allowed to prescribe drugs for off-label uses based on information already on the market, why not let them do the same for all drugs, at least if they have passed the minimum Phase I trials? The effort to create a sharp constitutional line between speech and conduct in this context fails, as it does in so many others. The same basic framework applies to both.

III. REMOVING OLD DRUGS FROM THE MARKET

Last, the role of rational basis review also arises in connection with many drugs that were brought to market between 1938 and 1962. As noted earlier, this was a period of heavy innovation. But it would be mistaken to assume that all licensed pre-1962 drugs remained in use thereafter. As Weinberger notes, about one-half those drugs were no longer in use. 78 So why? At the global level, the simple truth is that FDA drug approval never guarantees market acceptance. Certain drugs are hard to tolerate; others are approved but then displaced by newer drugs with fewer side effects; some conditions are better treated by nondrug methods. Innovation and attrition exert a high level of post-approval scrutiny and review.

The question then arises: How effective is that second screen? In this regard, the judicial decisions that have dealt with the construction of the 1962 Act have uniformly taken the FDA’s position that even when the law speaks of GRASE, it in fact allows the FDA to demand that old drugs be subjected to more exhaustive clinical trials. The striking disjunction between ordinary language and statutory language is made very clear in (then) Judge Breyer’s influential opinion in United States v. 50 Boxes More or Less, 79 which involved an FDA seizure—hence the 50 Boxes—of “Cafergot P-B Suppository, a drug that contains two active ingredients (caffeine, ergotamine) designed to stop vascular headaches, such as migraines, and two other active ingredients (pentobarbital, bellafoline) designed to stop nauseous side effects resulting from the first two ingredients.” 80 As Judge Breyer noted, in statutory construction things are not

78. See supra note 41 and accompanying text.
79. 909 F.2d 24 (1st Cir. 1990).
80. Id. at 25.
often as they seem. The suppository was a new drug even though it was widely
and successfully sold in the market place for over thirty-five years. It was lawful
to sell their components separately. In addition, Sandoz, its manufacturer, was
prepared to offer a wealth of expert evidence that its drug had proved safe and
effective over its long period of use. But it was all to no avail.

The ultimate justification for the decision rested on the general police power
justifications offered in *Weinberger* and the correlative deference to FDA. But
why? This suppository was a combination of two old drugs that could be taken
separately. Many drugs fall into that class, and the problem is so important that
just recently the FDA issued new guidelines as to how these drugs are to be
evaluated.\(^8\) The basic principle here is that the compound has to be tested even
if its components are safe. But note that this argument assumes again that
clinical trials are the only form of reliable evidence that deals with drug
safety—an assumption that is falsified by the extensive and successful off-label
use of many compounds.

Indeed, the case against the FDA’s standard depends on the unavoidable
weaknesses of clinical trials. One key limitation of clinical trials is their
comparative shortness. Even the FDA knows that it cannot tie up drugs forever,
so consequently some drugs will reach the market even with some residual risk
of some long-term effect that could alter the cost/benefit balance. But drugs
have to be approved sometime, which means that the available data does not
speak to long-term risks, which are typically evaluated by private organizations
like NCCN that regularly review and update information. It is critical in this
case to understand that the information needed to practice medicine well is
not found in some simple yes/no answers, but instead it requires a full and
up-to-date account that allows for rational downstream choices.

A second key limitation is that the sample sizes available in clinical trials are
limited both by the availability of patients and the costs of conducting clinical
trials. Given the number of potential drugs to test, and the ever more exacting
FDA standards, many clinical trials done under FDA supervision of necessity
involve the use of foreign data, but that data is only introduced when collected
by sponsors of clinical trials under FDA supervision.\(^8\) It is not possible to
introduce to the FDA evidence that foreign governments collect for their own
work, or to introduce the accumulated evidence from world-wide practice,
which helps drive off-label usage. Hence, two vital sources of information fail
to meet the FDA standard of what counts as valid scientific evidence, given
differences in clinical conditions and study populations. But it is irrational to

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count this evidence for naught, given that everyone has strong incentives to uncover failed drugs.

The result is especially galling for compound drugs because there is good reason to believe that they are often safer than the two drugs taken separately. The use of the compound pill adds another option for physicians in treating patients. In many instances, this option could prove exceedingly valuable because the dispensing of a single drug whose active ingredients are in fixed proportions reduces the likelihood of error in administration. Getting drugs in the right balance to sick patients of limited competence is often a very difficult task requiring extensive on-the-ground supervision. Hence any innovation that reduces this source of cost and error is a clear blessing. To be sure, the same ratios may not work in all cases, which is why the ability to prescribe both drugs separately still makes sense. But knowing the underlying situation, it is fair to ask just what information gap is filled by demanding a new round of clinical trials. If the original trial does not look for interactive effects, why do so here, when these would surely be evident from the high levels of use. The only conceivable issue could be the stability of the combined molecule, which seems like a thin reed on which to rest demands for clinical trials.

Recall the nature of the inquiry. Stable use is what clinical trials are supposed to establish. But when it is established by other means (such as through regular off-label use, for which data is available, or at least potentially available), the FDA's discretion only reduces choice, adds cost, and perhaps results in a decline in health for the potential patient population. It is not too much to demand that the FDA produce by its own efforts some independent evidence of a breakdown, at which point the drug is likely to be already pulled from the market. Yet given the wholesale disregard of all relevant institutional factors, FDA regulation on this topic, as on others, shows not the slightest awareness of the relevant trade-offs. It is, of course, always possible to ask, under the current capacious standards of rational basis, whether the accumulated sins of professional management matter, so long as there are some cases where clinical trials make good sense. But in my view, it cannot be rational to adopt any procedure that looks to be both more costly and less reliable than any other. It is not rational to place exclusive reliance on clinical trials whenever abundant supplementary evidence is at least of equal quality, if not more so. Even under our bizarre rational basis jurisprudence, it seems systematically perverse to place new obstacles in the path of drugs long on the market.

In the end, if it is necessary to shoehorn these cases into the rational basis category, it should be done here. But, alternatively, given that the FDA operates coercively, the rational basis test should be consigned to the dustbin of history. Either way, the FDA monopoly over drug access should be curtailed.

CONCLUSION

In dealing with political and social institutions, we must grapple with two fundamental issues: power and information. The FDA is a government agency
designed to protect the public. It should use its power to curb fraud and deception by private parties. It should not use that power to control either private behavior on individual health matters or private access to information about drugs and devices—information for which there is a huge demand. With both access and information, the government operates as a regulator, not a manager, so something like the business judgment rule is far too forgiving a standard for evaluating its conduct. A fortiori, the rational basis test, which is even more lenient, is not an appropriate standard for constitutional oversight. In dealing with new drugs, the FDA claims the power to override individual judgments on matters of health and safety. It cannot do so to protect public health because there are no risks of contagion or communicable diseases. If the decision to turn down treatment is deeply personal, so too is the decision to accept that treatment. In both contexts, a heavy burden lies on the government when it wishes to restrict a fundamental personal liberty. In connection with the FDA’s chokehold over new drugs, that burden cannot be discharged. The rules on clinical trials ignore too much evidence and act as though the standard rules of medical inquiry, used with respect to off-label drugs, are beyond redemption. And its effects of throttling the dissemination of relevant information have, and should, fall to First Amendment challenges. But so too should its coercive restrictions on sale and use. This extraordinary use of government coercion should not be subject to benign judicial oversight under the rational basis test. The FDA should always be allowed to state, in whatever terms it chooses, its objection to various courses of action. But advice is one thing; coercion is another. Right now there are curbs on its ability to prevent the free flow of truthful information. The next step is to remove its power to keep desperately desired clinical treatments off the market.