

**Balancing Government Regulation Against Access to
Drugs: Address to Seton Hall University
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It is a great honor for me to be invited to address this conference and to share my perspective as the General Counsel of the Department of Health and Human Services on the issues that you are discussing today.

Not having any particular personal or institutional expertise in intellectual property law, the portion of the theme of today's conference that I will address is the delicate balance between the FDA's regulations and approval processes, and public health and drug access concerns. The question that is the theme of today's conference is particularly timely for discussion at a legal conference. In the last few months, two federal court decisions have raised questions about the FDA's ability to serve as a gatekeeper over access to drugs in the market as well as to the propriety of the FDA's role in making determinations that limit the availability of new drugs to patients.

The first case to which I am referring, of course, is the *Abigail Alliance* decision.¹ As I am sure you are aware, in *Abigail Alliance* the D.C. Circuit announced a fundamental un-enumerated right, as part of substantive due process, "of a mentally competent, terminally ill adult patient to access potentially life-saving post-Phase I investigational new drugs, upon a doctor's advice"—that is, a constitutional right to drugs that the FDA has determined are safe enough to proceed to Phase II clinical trials but that are unapproved and that a doctor concludes are in the patient's interests.

I confess that when I first read the decision, my immediate thought was that it had been too long since I had taken Constitu-

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¹ *Abigail Alliance for Better Access to Developmental Drugs v. Von Eschenbach*, 445 F.3d 470 (D.C. Cir. 2006). Since this address was written, the D.C. Circuit issued its en banc decision affirming the District Court judgment dismissing the *Abigail Alliance*'s claims. *Abigail Alliance for Better Access to Developmental Drugs v. Von Eschenbach*, No. 04-5350, 2007 WL 2238914 (D.C. Cir. Aug. 7, 2007).

tional Law in law school, because I didn't recall reading the phrase "post-Phase I clinical trials" in the Constitution, nor, come to think of it, any mention of the FDA (which I'm sure was a drafting oversight by our Framers).

In fairness, however, one has to acknowledge that the decision by the majority in *Abigail Alliance* appeals—even if it doesn't expressly invoke—at least superficially, to principles that lie at the core of the political philosophy of our founding. Certainly, we all know that Hobbes and Locke and other similar social contractarians argued that people have a natural right of self-preservation. Locke went so far as to call self-preservation a "duty owed to God." And the drafters of our Declaration of Independence proclaimed that when "government becomes destructive" of these ends it is the right of a people to alter or abolish their government. The charge that limiting access to drugs outside of clinical trials to those drugs that have been approved by the FDA is violative of a fundamental right of self-preservation is, to say the least, an explosive one to make.

Upon closer examination, however, I would argue that the reasoning of the panel majority in *Abigail Alliance*, which closely follows the arguments made by the Alliance in that case, is philosophically incoherent. The *Abigail Alliance* court based its analysis on two main prongs: the relatively minimal history of drug regulation prior to the twentieth century (which, incidentally, I believe is somewhat exaggerated), and the common law tradition which recognized a right to act in self-defense. The panel, however, stopped short of the conclusion that one might have thought would have logically followed from its premises: that individuals battling potentially terminal illnesses have a right to make their own decision about whether to take drugs that may or may not be effective and that might or might not harm them. Instead, the panel held only that terminally ill individuals had a "fundamental right" to access drugs that both the FDA has determined are safe enough to proceed to Phase II clinical trials and that the patients' doctors had recommended. In other words, the Court accepted that the FDA may—notwithstanding statements in the opinion suggesting that the decision to take a drug that might save a patient is an area of personal autonomy that historically has been free of governmental regulation—bar access to unapproved drugs that the FDA deems not sufficiently safe.

But what, one may ask, is the principled constitutional distinction at work here? Once one accepts the principle that the FDA may constitutionally serve as a gatekeeper and prohibit provision of drugs that the FDA determines are not safe enough, what constitutional

significance is there to the difference between the standards of safety that the FDA applies in making determinations whether the drug may proceed to Phase II trials, versus Phase III trials, versus the ultimate drug approval decision? For that matter, why condition the exercise of this alleged fundamental right on a doctor's approval? Fundamental rights are generally understood to be rights to act free of government interference. Defining the very right by reference to an FDA regulatory scheme makes little sense.

For these reasons, although the *Abigail Alliance* panel, as well as the plaintiffs, insisted they were applying a fundamental rights analysis, it seems far more coherent to understand the analysis in *Abigail Alliance* as a form of very heightened rational basis or "arbitrary and capricious" review. In effect, the plaintiffs and the panel majority argued that it is irrational to have a regulatory scheme in which the FDA makes a determination that a drug is safe enough to be administered in Phase II clinical trials, yet to deny access to those same drugs to terminally ill persons who do not qualify or were unable to obtain a spot in the trial.

But under rationality review, this challenge must surely fail as well. Where there exist strong competing rationales pointing in different directions, the work of reconciling those competing policies when it comes to the regulation of commercial conduct is surely the job of regulators, not judges. Here, the FDA has strong interests in limiting clinical access to drugs that have not yet completed the clinical trial process, and those interests extend well beyond the paternalistic one of trying to protect the safety of patients. For example, patients who agree to participate in a clinical trial have approximately only a fifty percent chance of actually being administered the drug being tested; the remainder get either a placebo or an alternative treatment. Why would patients agree to participate in clinical trials if they could obtain drugs outside the clinical trial without that fifty percent risk?

Having said all this, there is much less here than meets the eye, in at least two respects. First, the FDA already has in place a procedure, now codified in the Food, Drug, and Cosmetic Act, by which terminally ill patients who wish access to experimental drugs outside the context of a clinical trial may obtain access to such drugs. In particular, section 561 of the Food Drug and Cosmetic Act (FDCA) permits individual patients to obtain access to investigational drugs or devices if (1) their physician determines that there is no comparable or satisfactory alternative therapy for the serious disease and that the risks of the investigational drug or device are comparable to the risks

of the disease or condition; and (2) the FDA determines that there is sufficient evidence of safety and effectiveness to support the use and that the use will not interfere with completion of clinical trials, and the sponsor submits an appropriate protocol. Section 561 further authorizes widespread access to investigational drugs where the FDA makes findings that the sponsor is proceeding with clinical trials and is actively pursuing marketing approval. With respect to individual patient requests for access to unapproved therapies for terminal or life-threatening conditions that are unresponsive to available therapy, the FDA has been quite permissive in its approvals. And while the FDA's rules prohibit manufacturers from charging such patients more than regulatorily defined "direct costs," that restriction is a perfectly reasonable way of both protecting desperate consumers and ensuring that manufacturers retain the incentive to pursue approval through the clinical trial process.

Second, there is of course no guarantee that removal of the prohibition of a manufacturer's supplying drugs outside the clinical trial process would in fact result in the manufacturer actually making the drugs available. This is a point to which I will return later.

The second recent court case, *Medical Center Pharmacy v. Gonzales*,² currently on appeal to the Fifth Circuit, squarely raises issues relating to the balancing of FDA regulation and access, challenging the FDA's authority to subject drug compounding to the Act's requirements relating to approval of "new drugs."

Drug compounding refers to the process by which a pharmacist or doctor combines, mixes, or alters ingredients to create a medication tailored to the needs of an individual patient. Compounding is typically used to prepare medications that are not commercially available, such as medication for a patient who is allergic to an ingredient in a mass-produced product. It is a traditional component of the practice of pharmacy. Although with the rise of modern manufacturing practices for drugs pharmacy compounding is less widespread, it is still a component of the practice of pharmacy and is taught as part of the standard curriculum at most pharmacy schools.

The FDCA, however, requires that the FDA specifically approve every "new drug" introduced into interstate commerce. The FDCA defines the term "new drug" as any drug the composition of which is not generally recognized as safe and effective, and there is little doubt that compounded drugs clearly fall within this definition and are therefore subject to the FDA's jurisdiction. However, were the

² 451 F. Supp.2d 854 (W.D. Tex. 2006).

FDA to require that every compounded drug be reviewed for safety and effectiveness, the practice of compounding would be effectively shut down. For that reason, the FDA traditionally left regulation of compounding to the states. Pharmacists continued to prepare compounded drugs for specific patients without applying for FDA approval of those drugs.

In the early 1990s, however, the FDA became concerned that some pharmacists were engaged in large-scale manufacturing under the guise of compounding, thereby avoiding the FDCA's new drug requirements. In 1992, in response to this concern, the FDA issued a Compliance Policy Guide (CPG) which announced that the FDA would continue to exercise enforcement discretion with respect to traditional drug compounding. However, if the manufacturer's compounding activities were akin to drug manufacturing, the FDA would consider enforcement actions.

The FDA's policy was largely codified by Congress in the Food and Drug Administration Modernization Act of 1997 (FDAMA), which contained a statutory exemption for certain drug compounding activities.³ The FDAMA provisions permitted compounding by a licensed pharmacist or physician in response to a valid prescription for an identified individual patient, or, if prepared before the receipt of such a prescription, in "limited quantities" only. The statute also prohibited pharmacies from soliciting prescriptions and from advertising the availability of specific compounded drugs. Pharmacists could advertise their compounding services generally, but not specific compounded drugs.

These speech restrictions were challenged by a group of pharmacists on First Amendment grounds in *Thompson v. Western States Medical Center*.⁴ The case made its way to the Supreme Court, which held that the speech provisions in FDAMA were not narrowly tailored to promote the government's objectives, and thus unconstitutionally restricted the speech rights of pharmacists. Interestingly, in that litigation, the Ninth Circuit Court of Appeals held that not only were the speech restrictions unconstitutional, but that they could not be severed from the other provisions of the law relating to compounding. Therefore, according to the Ninth Circuit, the entire compounding section of the statute was invalid. That issue was never appealed to the Supreme Court, and thus the Supreme Court did not rule on severability.

³ 21 U.S.C. § 353a (2000).

⁴ 535 U.S. 357 (2002), *aff'g* *W. States Med. Ctr. v. Shalala*, 238 F.3d 1090 (9th Cir. 2001).

Following the *Western States* litigation, the FDA has taken the position that the FDAMA provisions relating to compounding are invalid, and has issued a revised compliance policy guide that sets forth the circumstances under which the FDA will exercise its enforcement discretion to permit compounding of specific drugs. The FDA's approach is again based on balancing access and safety—permitting compounding in limited quantities in response to a specific, valid prescription from a physician. But when the volume or other circumstances of compounding suggest that the pharmacy is actually acting as a drug manufacturer, the FDA will consider enforcement actions.

In particular, the FDA's CPG defines traditional compounding, which the FDA leaves for the states to regulate, as the "extemporaneous[] compound[ing] and manipulation of reasonable quantities of human drugs upon receipt of a valid prescription for an individually identified patient from a licensed practitioner."⁵ When considering potential enforcement actions over drug compounding, the FDA has stated it would take into account the following: whether the compounding was being conducted with drugs that were withdrawn or removed from the market for safety reasons; whether compounding created finished drugs from bulk active ingredients that were not components of approved drugs; whether the compounding used commercial scale manufacturing or testing equipment, and similar indicia of potential harms. In short, we are fully aware that there are many beneficial instances of compounding, and that it would be bad policy to prohibit all forms of compounding. The FDA is committed to making sure that its enforcement guidance is clear enough to avoid deterring beneficial conduct, while at the same time making sure that abusive practices involving bulk compounding remain subject to its enforcement.

The district court's decision in *Medical Center Pharmacy* throws much of this conceptual framework into doubt, although the district court's injunction did not permit wide-scale compounding in bulk. The district court concluded that, contrary to the Ninth Circuit's holding, the majority of section 503A remains valid, and that the FDCA implicitly excludes compounded drugs from the definition of "new drugs." While reasonable people might disagree on the severability issue decided by the Ninth Circuit, I believe that section 503A actually confirms that Congress intended compounded drugs to qualify as "new drugs," because otherwise its express exemption of drugs that are compounded individually under the conditions specified in

⁵ U.S. FOOD AND DRUG ADMIN., COMPLIANCE POLICY GUIDES MANUAL § 460.200 (2002), http://www.fda.gov/ora/compliance_ref/cpg/cpgdrg/cpg460-200.html.

section 503A from the definition of new drug would have been unnecessary. This case is now on appeal to the Fifth Circuit, and we hope that the Fifth Circuit will place the task of balancing the competing risks and benefits of compounding back at the FDA—where it belongs.

Perhaps the most fundamental and visible example of the balance of government regulation and access is the continuing debate over the speed of drug approval by the FDA and the availability of resources for that purpose. Since 1962, the FDCA has required the FDA to assess the safety and effectiveness of every new drug before it may lawfully be distributed in interstate commerce. The statute requires manufacturers to provide the FDA with extensive data demonstrating that the drug is safe and effective and that the product can be consistently produced within precise specifications. The FDA is required to review all of the data submitted by the manufacturer and determine whether the product meets the statutory standards for approval. This takes time and resources. For that reason, there has long been controversy surrounding the length of the FDA's review and the resources available to the agency to review applications.

In 1992, for the first time, Congress authorized the FDA to collect fees from drug companies to fund drug reviews. The Prescription Drug User Fee Act (PDUFA)⁶ established a system whereby manufacturers were required to pay significant fees to the FDA for the review of both initial applications for the approval of a new drug and subsequent supplemental applications, such as an application for an already approved drug to be approved for use in a new indication. PDUFA was authorized by Congress for five years, and it has been reauthorized twice—in 1997, then again in 2002. PDUFA is up for reauthorization this year, and once again, the debate has centered on FDA resources, review times for drug applications, and drug safety.

When PDUFA was first enacted in 1992, the focus was speeding up the review time for drugs. At that time, many felt that the FDA was not approving new medications fast enough, particularly for diseases such as AIDS and cancer. Accordingly, under the original enactment of PDUFA and subsequent reauthorizations, PDUFA fees were meant to facilitate and speed drug reviews. Under the law, the FDA must render a decision on a new drug application within ten months. The FDA can request additional data or take other actions to extend the clock on action dates, but generally speaking, PDUFA has had the effect of dramatically shortening review times for drugs.

⁶ P.L. 102-571, 106 Stat 4491 (1992).

In addition, PDUFA mandated that the FDA hire additional staff dedicated to reviewing applications.

Under current law, PDUFA fees can be dedicated to monitoring safety issues only for the first three years following approval of a drug. Clearly, the Congresses that enacted PDUFA I to III felt that the FDA was taking too long and erecting too many hurdles to drug availability. Today, the focus is somewhat different. Although facilitating efficient reviews of new drug applications remains a priority, there is a great deal more attention given to drug safety, and especially to the resources available to the FDA to engage in post-approval surveillance. Think of Vioxx or Ketek. Accordingly, as part of the discussion over the reauthorization of PDUFA this year, the FDA has proposed that the three-year restriction on use of PDUFA fees for drug safety monitoring be lifted, and that a significant portion of PDUFA fees be dedicated to post-market drug safety initiatives.

PDUFA, therefore, illustrates the careful balance that the FDA and Congress must strike—on one hand, providing speedy access to needed medications, but on the other hand, ensuring the continued safety of the U.S. drug supply. How the FDA and Congress strike that balance can shift over time, and we are currently seeing the pendulum swing towards drug safety.

Of course, no discussion of FDA regulation and drug access would be complete without some mention of the very public debate over drug reimportation. That debate goes directly to the question of the appropriate level of government regulation to balance competing goals—ensuring the safety of the drug supply and giving consumers greater access to affordable medications. The disparity of drug costs in the United States compared to other countries has led many to assert that the government should permit consumers to freely import drugs from other countries, Canada in particular.

Unfortunately, the debate over re-importation, in my opinion, has been marred by confusion of terms and misapprehension of the current legal requirements. Individuals debating the issue often talk past each other, because they use the same terms to mean very different things.

Of the various types of conduct to which one might refer, only one is strictly speaking re-importation, which is when a U.S.-manufactured drug, approved for sale in the U.S., is exported abroad and then re-imported back to this country. That is legal today, so long as it is the original manufacturer who does the re-importation. But that process does not result in cheaper drugs, and is not what most people mean when they use the phrase “re-importation.” It is of

course also legal for persons to *import* (not re-import) FDA-approved drugs made for the U.S. market in FDA-inspected foreign facilities—but again, this process doesn't result in access to cheap foreign prices.

Two main categories of importation are currently illegal. One is the importation of unapproved drugs produced in facilities that the FDA has not inspected at all. The second, and perhaps the one that has garnered the most attention on the part of advocates of liberalizing importation rules, involves foreign versions of drugs that are manufactured in the same facility (although often on a different production line), and by the same manufacturer, as the FDA-approved drug.

Proponents of liberalizing importation of this latter category of drugs from Canada helped secure passage of section 804 of the FDCA. That section, codified at 21 U.S.C. § 384, would allow drug wholesalers and pharmacists to import prescription drugs from Canada under certain circumstances. However, that section of the statute is effective only if the Secretary of Health and Human Services (HHS) certifies to Congress that the section's implementation will "pose no additional risk to the public's health and safety" and will "result in a significant reduction in the cost of covered products to the American consumer." To date, no HHS Secretary, going back to the Clinton Administration, has made such a finding.

Section 804, however, presents something of a legal conundrum. Even if a Secretary were to make the required finding, section 804 requires that importation only be permitted in accordance with regulations that "require safeguards" that each imported drug comply with section 505 of the Act (requiring FDA approval of the drugs as safe and efficacious) as well as with sections 501 and 502, which respectively bar drugs that are adulterated and misbranded. Enforcement of this requirement would virtually make a null set of drugs that could lawfully be imported from Canada, even if the Secretary were able to make the requisite certification. Drugs manufactured in Canada for the Canadian (or another foreign country's) market would not be packaged with U.S.-approved labeling, and would often not be produced on the FDA-approved and inspected manufacturing lines. Such drugs will, therefore, not be approved under section 505 (which requires approval of the labeling and production facilities), they will almost always be misbranded, and the lack of FDA inspections would make it impossible for the FDA to create safeguards that the drugs are not adulterated as defined by law. Although policy debaters often talk about modifying U.S. policy to allow importation of foreign ver-

sions of “FDA-approved” drugs, drugs manufactured for foreign markets are almost necessarily not FDA-approved, and the FDA cannot provide assurances as to their safety.

Conventional wisdom holds that FDA regulation has an inverse relationship with access to drugs—greater regulation reduces the availability and access to drugs. Up to now, I have focused on aspects of the U.S. regulatory system that might be consistent with that premise. But there is one very important context in which the conventional wisdom does not always hold, and in which FDA regulation may serve to increase access to drugs.

The FDA is not the only entity that establishes requirements pertaining to the design and labeling of drugs. The common law tort regime, usually implemented by lay juries, imposes its own form of after the fact “review” of the safety of drugs and of the accuracy of labels. Although prior Supreme Court decisions questioned this, the Supreme Court’s recent decision in *Bates*⁷ firmly recognized that awards under the common law impose “requirements” on manufacturers, as that term is used in many express preemption clauses. It is often argued that the threat of large damage awards diminishes the willingness of manufacturers to introduce certain categories of drugs to the market and increases the prices of those drugs that are introduced.

By removing the threat of inconsistent and burdensome state regulatory requirements that might otherwise apply to drugs, preemption works to increase access to prescription drugs. Were states to impose their own requirements on drugs, manufacturers would be required to comply with fifty different regulatory systems. This could mean substantially different versions of the labeling to be distributed with drugs, or even different methods of manufacturing the product in order to comply with state requirements. Were this to happen, manufacturers would face potentially prohibitive costs, and, in the extreme, could face a situation where they could not comply with both state and federal law. By operation of the preemption doctrine, the FDA’s regulatory requirements serve to remove inconsistent state requirements and establish a uniform national standard, thereby enhancing the availability and access of these products.

But the preemptive effect of FDA regulation is directly correlated to its intrusiveness. Where the FDA regulatory process includes detailed review and approval of specific designs and particular wording on labels, a process that is deliberate, methodical and time-

⁷ *Bates v. Dow Agrosciences LLC*, 544 U.S. 431 (2005).

consuming, courts have generally agreed that contrary state law tort verdicts are preempted. But where the FDA process has been streamlined, preemption is far less likely to be found. A stark demonstration of this is in the medical device context. In *Medtronic v. Lohr*,⁸ the Supreme Court held that the streamlined “substantial equivalence” 501k determination that the FDA makes in approving devices did not create federal requirements of preemptive effect. Yet, even after *Lohr*, six of the seven Circuits that have considered the question have concluded that the slower but much more rigorous pre-market approval process for devices did preempt state law defective design and misleading labeling claims.⁹ This is thus one area where increased FDA regulation can actually lead to greater access to more affordable therapies.

This last point brings us back full circle to *Abigail Alliance*. Even removal of the prohibition on access to experimental drugs would not impose any requirement that manufacturers actually make such experimental drugs available to patients. In fact, there is substantial reason to believe that manufacturers might not make their drugs available to patients outside the confines of clinical trials. Experimental unapproved drugs, by definition, have not been found safe and effective by the FDA, and thus the FDCA would not generally preempt tort claims against manufacturers by individuals injured by these drugs. Although manufacturers would undoubtedly try to limit sales to those who sign express and broad releases, their exposure in tort might very well have limited the practical effect the *Abigail Alliance* decision would have had.

⁸ *Medtronic, Inc. v. Lohr*, 518 U.S. 470 (1996).

⁹ The Supreme Court of the United States granted certiorari to resolve this circuit split. See *Riegel v. Medtronic, Inc.*, 451 F.3d 104 (2d Cir. 2006), *cert. granted*, 75 U.S.L.W. 3690 (U.S. June 25, 2007) (No. 06-179).