FDA INVOLVEMENT IN OFF-LABEL USE: DEBATE BETWEEN RICHARD EPSTEIN AND RYAN ABBOTT

Richard Epstein* & Ryan Abbott**

INTRODUCTION:

Dean Susan Prager (DP)[1]:

I want to begin by thanking the Federalist Society and the Southwestern Law and Medicine Society who joined together to bring us this wonderful event.

Professor Epstein is a true luminary in legal thought and has been for many decades. I want the audience to know that he had the wisdom to start his law career in southern California at USC, and left after a few years to join the faculty at the University of Chicago, and more recently he has moved to NYU. We are very grateful that you had the wisdom to travel to Southern California on this beautiful day.

Ryan is at the other end of the spectrum in terms of years of teaching. He secured his undergrad degree at UCLA, and then went to UC San Diego to medical school, and then to Yale where he earned his law degree. He brings legal and medical perspective to this debate. He is not only a professor at Southwestern Law, but he is also a visiting assistant professor at the David Geffen School of Medicine at UCLA.

Let me briefly mention a few things about the topic that these two gentlemen are going to discuss.

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1. Dean, Chief Executive Officer and Professor of Law, Southwestern Law School. http://www.swlaw.edu/faculty/faculty_listing/facultybio/340886.

Before a drug can be legally sold in the U.S., the Food and Drug Administration (FDA) must approve it as safe and effective for a particular use. That use then appears on the drug's label. Federal law enables doctors to prescribe drugs that the FDA has approved for one indication for any other indication, even though the FDA has never evaluated that drug for the safety or efficacy of that particular application. This is the so-called, "off-label" use, which is the subject matter of this debate.

However, when a physician prescribes off-label, that decision is to be left up to the physician—the law forbids drug companies from promoting their products for off-label use. This debate is about whether this is the appropriate framework that we should be pursuing as a matter of public policy. It is certainly the case that this framework is replicated in a number of other areas, and that will hopefully provide for you food for thought long after the debate. We're going to begin with Ryan and then we will move to Richard. The format will be that they will each address the issues for five minutes, and then they will have the opportunity to briefly rebut some of the elements of the other person's arguments.

We do have a timekeeper. I don't have a hook, but I can grab you if you go on too long. With that, Ryan.

I. DEBATE

Professor Ryan Abbott (RA):

The central problem with off-label drug use is that we have an information deficit. When the FDA approves a drug for on-label use, that approval is based on scientifically valid and statistically significant evidence that says, we are going to give you a drug, which is potentially dangerous, but it is likely that the benefits outweigh the risks. We know that because we have studied the drug in a controlled environment. That information is simply not available with off-label use.

Over 70% of off-label prescriptions used are not based on scientific evidence or significant scientific evidence.[2] That's a real problem because all drugs have a risk of serious side effects, and patients shouldn't be exposing themselves to risk without evidence that a drug will be effective. When evidence is available, it often is not at the level required for a new approval, and sometimes it is of very low quality. Frequently, you have physicians prescribing a drug because they think it will work or because they've heard from another doctor it might work, and they are informing their practice based on what they hear from select patients. That's how

2. Randall S. Stafford, *Regulating Off-Label Drug Use — Rethinking the Role of the FDA*, 358 NEW ENG. J. MED. 1421, 1427 (2008).

medicine was practiced a hundred years ago, and that's the worst kind of medical practice.

Also, no one is systematically collecting information on off-label uses and patient outcomes. For the most part, physicians are independently getting anecdotal reports from a biased sampling of patients – and even that information is not shared. So not only are patients using drugs we don't know are safe and effective, but we are not getting good feedback to inform future practice. On the other hand, we don't want to prohibit off-label uses because it is not ever going to be possible to study every drug for every possible use, and some off-label uses do have reasonable scientific support, and others have been around for a long time with reported benefit and few adverse events.

That is the off-label problem: How do we balance patient access with preventing harm, and what role should the FDA play? Right now, the FDA plays a minimal role and there is little government regulation in this area. Once a drug is approved, with a few exceptions, the FDA lets physicians use a drug however they want. In fact, we don't have enough regulation and we need to be thinking about new ways to get third parties involved in the process. But if you think we have too much regulation, its helpful to look back at history and see how we got here. Because a hundred years ago we had a system where there was no meaningful regulation and companies could market however they wanted. We got a series of tragedies ranging from Sulfanilamide, which led to the FDA evaluating safety, to Thalidomide, which lead to the FDA investigating for efficacy, to drugs like Vioxx, which was a driving force behind the 2007 FDA amendments.[3] All of these cases convinced the public that we need a centralized system and public oversight.

This march towards greater oversight has not been accidental, and the idea that we should return to an earlier period ignores or misinterprets history. History, as well as common sense, teaches us that we cannot just leave this for the market and after-the-fact tort liability to handle. We cannot regulate by having consumers reward or punish firms after-the-fact because of the human cost. If a bad drug hurts a patient, even if they were able to get compensation, and even if we could punish a company for bad behavior, that's not the kind of system we want to have. We want a system that prevents someone from being injured, rather than one focused on compensation. Furthermore, we don't have a health care market in which value-based competition occurs. Consumers are insulated from the price of

3. Ryan Abbott, *Big Data and Pharmacovigilance: Using Health Information Exchanges to Revolutionize Drug Safety*, 99 IOWA L. REV. 225 (2013).

drugs because of insurance, and they do not have good information on which drugs are better - not at least for most off-label uses - and certainly not for comparative effectiveness research between different types of drugs. So without good information on quality and cost you can't have meaningful competition.

So the FDA now restricts what pharmaceutical companies can say and that's a very wise policy, because even a cursory examination of the pharmaceutical industry shows that it is not an industry that will regulate itself. Pharmaceutical companies are in business to make money for their shareholders—which is fine—but they have incentives to oversell off-label uses that outweigh their potential liability. It can become a cost of doing business. In 2009, Pfizer was fined 2.3 billion dollars for off-label promotion of Bextra and three other drugs, but that was only 14% of the 17 billion it earned from selling those drugs. Also in 2009, Eli Lilly paid 1.4 billion dollars for illegally promoting Zyprexa off-label. By that time it had made at least 36 billion from that drug. Those are a couple of examples, but every major pharmaceutical firm has been prosecuted for illegal promotion. Firms have promoted based on selectively publishing favorable outcomes from poorly designed trials, funding consumer organizations to promote off-label use, and paying physicians to recommend off-label uses. Pharmaceutical company promotion is a very effective practice that has been shown to influence prescribing practices. It's not for nothing that the industry spent 27 billion on drug promotion in 2012, 24 billion of which went to marketing to physicians. These sorts of behaviors should be very concerning to regulators and to you because promoting off-label uses without evidence of safety and efficacy is more likely to result in significant harm and it wastes resources. One of the tenets of medicine is that doctors should first do no harm, which is why as a faculty member in the school of medicine I can no longer get free pens, or free lunches, or free trips to Hawaii from drug reps. And while that is very unfortunate for me—life is full of disappointment.

I only have 30 seconds remaining, so in brief, what should we do instead? A number of people have proposed that we strengthen our current system by, for example, enacting stricter criminal and civil penalties, by enhanced enforcement, by creating stronger firewalls between pharmaceutical companies and academics, and by always publishing full clinical trial data results rather selective data.

Ian Ayres and I have an article forthcoming in Duke Law Review on mechanisms for regulating off-label uses of drugs and devices.[4] We argue for improvements in reporting, testing, and enforcement regulations to provide a more layered and dynamic system of regulatory incentives. But, as I'm short on time, I'll refer you to read the paper if you're interested.

Professor Richard Epstein (RE):

I take a different view of this particular issue. Let me start at the beginning. There are two ways in which the government can oversee drug usage. One approach is to regulate drugs before they hit the market; the other is to wait until they are marketed, and then regulate them afterwards. The way in which Ryan put the issue makes it appear that there are relatively few errors that infect the pre-clearance mechanisms associated with the FDA, and, further, that most of those errors come from letting drugs on the market too rapidly. Some of us who work in the area take a different view: that the great problem with the FDA is that it keeps drugs off the market too long. So if you simply concentrate your attention on those particular drugs which are in fact in the marketplace after FDA approval, and ask how many years they were kept off the marketplace by virtue of the time it takes for pre-clinical and clinical trials, inspections and reviews, you realize that second kind of error is every bit as important. It is a serious error to keep valuable drugs off the market for too long. It turns out that this very costly logjam has only gotten worse in recent years. It takes well over a billion dollars today, and probably seven or eight years of clinical trials, before a drug manufacturer introduces a new product onto the marketplace. That one fact means that the rate of new drug introduction into this country is very low, such that many drugs are not available today in this country even though they are in fact available elsewhere throughout the world, where the regulatory entry barriers are much lower and much less destructive.

Now, once it becomes evident that the spigot on new entry is kept too tight, desperate and ingenious people, facing serious medical conditions, are going to seek out alternative paths to get what they perceive to be better medical treatment. On this particular point, it becomes critical to understand something about the scope of off-label uses. If you are starting to talk about cancer drugs, for example, nobody knows the precise numbers but off-label use may be as high as between 75 and 90 percent of total drug use. Cut it down substantially, and the usage rate is still very significant. Most of that

4. Ryan Abbott & Ian Ayres, *Evidence and Extrapolation: Mechanisms for Regulating Off-Label Uses of Drugs and Devices*, 64 DUKE L. REV. 377 (2014).

use takes place without illegal promotion by the drug companies, when physicians decide for one reason or another that they are better off using an off-label use than having a patient die when the existing treatments are known to be ineffective.

The question then, for these off-label uses, is how does a conscientious patient decide which of these drugs to use and why. What Ryan said is not in my view an accurate account about how the mechanism works. Of course, there is a little bit of hearsay and happenstance: "hey, I tried this on patient 'X' and it seemed to work well, why don't you try it on patient 'Y.'" But the need for good information on drug choice is so important that both informal organizations and formal organizations have emerged to serve as intermediaries between individual physicians on the one hand and the drug companies on the other.

For example, there is an organization known as the NCCN, the National Comprehensive Cancer Network. This is a voluntary organization, and what it does is collect information about the various uses of the many drugs now available on the market, including their off-label uses. The organization is much more efficient and much more rational than the FDA, which is terrible in its approval process. Unfortunately, the only thing the FDA approval signals is that the manufacturer can sell the drug, assuming it can find a buyer. But for drugs licensed for sale, the FDA typically requires a set of patient and physician warnings that are heavily weighted towards the risks associated with the drugs, so much so that it could discourage patient from using drugs, which in fact have positive expected value for the patient. So there is a widespread practice among individual physicians to disregard or downgrade the FDA warnings by relying instead on warnings and information generated by independent physicians working collaboratively.

What do these physician networks do? They operate a fairly comprehensive basis. They get real time data not only from the use of drugs in the U.S., but also from the use of these drugs around the world. When they start to make their recommendations, they don't simply say this drug is or is not approved. They also undertake two other tasks of vital importance for sensible drug use. First, they rank drugs in order of their desirable use. In dealing with cancer patients, for example, the intermediaries specify first-line treatments and second-line treatments and so forth down the line. It is extremely important to know in what sequence these drugs should be used. The FDA provides doctors and patients with no information of value on this particular issue, but the NCCN and the four or five other organizations that work in this same space do supply extremely useful information on the ways in which these drugs work.

The second point to note about the FDA approval process is that it simply looks at drugs in isolation. The FDA does not talk about what combination of two or more drugs may be more efficient than the single use of any approved drug. That information is so valuable that it shapes modern practice and facilitates off-label uses. The current system would collapse without this safety valve from the current FDA system of drug regulation. Thank you.

RA:

Let me start with Richard's comments on informal or formal organizations versus the FDA. First of all, I am certainly not against voluntary organizations like NCCN compiling and disseminating information. I think it's very helpful. Although, I think it's a very real concern that a number of these organization, and I'm not specifically referring to NCCN, have industry funding and that one should be very suspect of that. When you are comparing voluntary organizations to the FDA, one of the great benefits of the FDA is transparency. The FDA now has very stringent conflict of interest rules and disclosure requirements. Private organizations are often not upfront about that sort of thing.

The idea that voluntary organizations are better suited to regulate than the FDA - I strongly disagree with for several reasons. First, private organizations generally have ad hoc funding. The FDA's budget this year is five billion dollars. It is large institution with significant technical expertise. Private organizations frequently lack that expertise, and they often depend on volunteer experts. Those private organization's compendia have been criticized by a number of academics. The information disseminated by the FDA is far more accurate and comprehensive than the compendia. Also, the FDA has better access to data. The agency requires pharmaceutical companies to report adverse events to the FDA. It can demand patient source level data from pharmaceutical companies – that is, the actual data from clinical trials, rather than what researchers choose to report. The FDA has data sharing agreements with foreign regulatory agencies, and so they do look at data from other countries. They can tap into clinical datasets from Medicare and Medicaid, the Veteran's Administration, and other public health care entities. They have the Sentinel Initiative, which can access data on over 130 million U.S. patients from private insurer data partners. They have an adverse event reporting system that physicians and patients can report to.

In sum, they have vastly superior data and superior resources. They are the only organization that can require pharmaceutical companies to conduct

post-market studies if they detect an unexpected serious risk.[5] So while I think it's important that we have voluntary organizations, and while I think there is a greater role for private organizations, I do not think it is possible that they can replace the FDA.

Richard referred to the oncology sphere. That is one of the areas of medicine where there is a very high level of off-label use. About 20% of all prescribing is off-label, but as he mentions, with cancer treatment it can be as high as 50% or even 90% in certain areas where people have rare types of cancer and where there is really weak research.[6] But that fact cuts against his own argument that pharmaceutical companies should be responsible for disseminating information. The physicians treating in these settings are very sophisticated oncologists who are often in academic settings. Those doctors are savvy about seeking information on off-label uses, and frankly, they do not need pharmaceutical reps educating them. They are able to get the information they need independently, or even from private organizations and compendia.

The 1.3 billion dollar figure he gave as the cost of bringing a drug to market is a very controversial number that comes out of an industry-funded study. The industry is not transparent about its costs, and other academics have estimated the costs of bringing a drug to market are far more modest – depending on the drug in question. If it's a me-too drug, which is drug that is similar a drug already being marketed, the costs of bringing it to market are comparatively minimal. In terms of the approval timeline, just this month, in January, there was a new article out in JAMA Internal Medicine that looked at all the drugs approved in 2008. On average, it took six and half years for a drug to be approval from the time when the FDA approved clinical trials. The FDA spent an average of ten months reviewing a drug's application. Further, the agency has a number of accelerated approval programs that significantly shorten that timeframe.

With regard to pre-clearance errors - briefly, the FDA requires three sets of trials prior to a drug being approved: phase I, phase II, and phase III trials. Phase I trials are very small: groups of patients 20-80, often healthy volunteers. Phase II and III trials are often in much larger patient groups. The FDA usually requires all trials phases prior to approval. Most the drugs that are in Phase I trials don't ever make it out, and that is because these clinical trials show that the drugs are not safe or effective for their intended

5. Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85, 121 Stat. 823, § 901 (a) (2007). The agency can require post market studies to assess a known serious risk, to assess signals of a serious risk, or to identify an unexpected serious risk. *Id*.

6. Stafford, *supra* note 3, at 1427; Marc A. Rodwin, *Rooting out Institutional Corruption to Manage Inappropriate Off-Label Drug Use*, 41 J. L. MED. & ETHICS 654, 656 (2013).

use, and all drugs are potentially dangerous. Patients should only be taking these drugs if we have good evidence that they are likely to produce more benefit than harm. The idea that we should just let all these drugs out and let people experiment on them turns the population into a bunch of guinea pigs. Perhaps there is a certain amount of that, but at the very least pharmaceutical companies shouldn't be promoting their own drugs for that purpose, and they shouldn't be allowed to oversell their benefits and down-play their risks. Again, there are an endless number of cases where that has occurred, and where patients have been seriously injured.

Thalidomide is an example. That was a drug in approved and used in Europe as a sedative hypnotic. Then the manufacturer started marketing it for morning sickness. No one stopped them from doing that in Europe, and soon it was being used worldwide. But the FDA kept it from being used in the U.S. because the drug company had not conducted any research with pregnant women, or even with pregnant animals. Sure enough, thousands of infants were killed and thousands more suffered severe birth injuries. That was a case of a manufacturer promoting its drug for an off-label use where it wasn't safe and hadn't been adequately studied.

RE:

Thalidomide is, of course, on the market today. It is a drug called Thalomid. And it is used to treat leprosy and a whole variety of conditions. But one of the things you have to understand is that there are many different propositions in play here. One possibility that I am not urging now, although I have considered it elsewhere,[7] might one to fundamentally restructure the FDA approval process. But in this context, remember that an off-label drug has gone through a Phase I trial already, which indicates very clearly that the drug does not have highly toxic effects. Its final approval also means that it has also been found valuable for at least some diseases. So that when a physician decides to try it for an off-label use, he or she has access to a much larger set of information than is available for a drug that has not been tested for any purpose at all. So one cannot infer that there is no information on which to base the decision to try the drug. Secondly, there have been huge amounts of these off-label uses. If in fact they were as deleterious as one might fear, you would expect to see some serious reconsideration of these uses especially if some clinical studies reveal that they have high levels of toxicity and other dangers. But as best I can tell

7. Richard A. Epstein, *Against Permititis: Why Voluntary Organizations Should Regulate the Use of Cancer Drugs*, 94 MINN. L. REV. 1 (2009).

typically there has been no definitive study of those potential dangers from off-label uses. Prior FDA approval thus changes all the calculations

The next point that I did not talk about earlier is drug company promotion with respect to off-label uses. I talked about promotion by independent agencies. Now, when you talk about the FDA, its incompetence in handling many drug applications is quite legendary. I can give you chapter and verse of people who have gone there and what they report. Typically the FDA has one or two experts per field, for example in cancer. Yet all the doctors and research scientists from the drug companies that come before the FDA have much narrower and much deeper levels of expertise. There is a mismatch of expertise that leads the FDA to drag out proceedings with endless requests for more papers and more tests.

Next FDA delay imposes an extremely important cost. For example, there are organizations out that have advocated particular drugs for many years, and virtually every single one of those eventually makes it on the market. But a delay of one, two, even five or six years is critically important. People, who could be helped, die in the interim.

In seeking FDA drug approval, one reason the cost can reach 1.2 billion dollars is the need to invest money on basic studies and clinical trials early on in the process. That requires it to include the cost of capital for drug development as part of the cost. The critics tend to ignore that cost, most notably in by the late Arnold Relman and Marcia Angell, who, knowing nothing about finance, concluded that these capital costs should not be included in total cost, on the novel ground that pharmaceutical companies have no alternative but to invest in research if they are to remain in the business.[8] Corporations, it seems, do not bear the costs incurred by ordinary people. Doctors should stick to their areas of expertise.

Next, I think that Ryan's point about conflicts of interest gets it exactly backwards. One of the problems that you have with the FDA is that it refuses to allow anyone with industry connections to sit on any panel to deal with any drug.[9] So what the FDA does is restrict itself a very small subset of people. Most competent experts do some degree of consulting. Since they are excluded, these FDA committees have very high vacancy rates and lower than necessary average quality. All of its bureaucratic

8. Arnold Relman & Marcia Angell, *America's Other Drug Problem: How the Drug Industry Distorts Medicine and Politics*, THE NEW REPUBLIC, Dec.16, 2002, at 27, 29. The $802 million figure comes from the highly cited article, Joseph A. DiMasi, Ronald W. Hansen & Henry G. Grabowski, *The Price of Innovation: New Estimates of Drug Development Costs*, 22 J. HEALTH ECON. 151 (2003).

9. Richard A. Epstein, *How Conflict-of-Interest Rules Endanger Medical Progress and Cures*, MANHATTAN INST. FOR POL'Y RES. (2010); *see also* Richard A. Epstein, *Conflicts of Interest in Health Care: Who Guards the Guardians?*, 50 PERSP. BIOLOGY & MED. 72 (2007).

expertise works to the serious disadvantage of FDA operations. It is morbidly inefficient. It is rigid. It is outdated. It is simply unable to deal with problems of personalized medicine, which by definition does not rely on large clinical trials.

It gets worse. The FDA doesn't know how to take into account evidence that you get from use in the field. It does not consider foreign experience. And as I mentioned before, it doesn't take into account drug interactions and so forth. Its warnings are almost always too severe for the problems at hand. The organization is not a model of what modern medicine needs. The FDA rests on a model that might have worked for 1950s, 1960s medicine. It certainly does not work today. In fact, the 1962 Kefauver-Harris bill, which was passed in response to Thalidomide tragedy, addressed an issue of effectiveness, which is controlled by other forms of regulation. The effect of the 1962 legislation over the next twenty after passage was to force dozens of drugs with long satisfactory histories of consumer use off the market, because no one could afford to send them through major clinical trials.

In sum, you are looking here at regulatory system that is seriously broken. Off-label use is an essential correction for the bad type outcomes of the preapproval process. Do not assume that FDA administrators actually know what they are talking about solely because they insist that they are in favor of protecting the public. In many cases, it turns out that they are wrong or uneasy. Their insecurity leads them to demand more and more clinical trials. This move raises costs and slows down innovation. The interaction between the shortened patent life on the one hand and costly FDA approval has dulled innovation. The number of new drugs that get through has fallen consistently over the last several years.

The U.S. is not itself a model of good sense and good judgment on any of these key issues. We ought not to think of the FDA as though it were an exemplar. What we should remember is that all administrative agencies have their own bureaucratic imperatives. By no stretch of the imagination are they faithful agents for the public interest, given their own bureaucratic imperatives. The FDA gets slaughtered if it lets a drug on the market, which turns out to have adverse side effects. It suffers no rebuke if it keeps some new drug off, even if it is likely to prove very safe. Its incentives for excessive caution tend to lead to wrong choices that distort market behaviors.

DP:

One of you mentioned the fact that drugs are available in other parts of the world. In this increasingly global society what are the implications for the topic you're addressing?

RE:

Okay look, one of the things you have to understand is that there is an inherent series of biases associated with clinical trials. First, they have to be relatively short, so often times when you are worried about a long-term adverse effects, which you can't pick up by simply increasing the dosage over a shorter period of time. If you have foreign field data available it may help supply the long time horizon to fill the gap in clinical trials. But that evidence is generally ignored.

Second, recently the FDA makes heavier demands that clinical trials be done on ever smaller groups of the population, so you have can pick up racial differences, pregnant women, different age cohorts and the like. The goal is laudable, but the shrinkage in the number of suitable subjects available to run a robust clinical trial slows matters down further. These trials also only start at fixed points in time, so its not just a question of identifying people with, say, type II lymphoma. You have to be able get those people into the study as of a particular date in order for clinical trial to work. So the whole system is broken down.

Third, let me just make it clear that drug companies are often complacent in attacking the FDA because of their divided motives. On the one hand, they make drugs that are currently on the market, and are therefore quite happy to see a new competitive drug kept off the market because that postponed entry increases the economic life and economic value of its current drug. The people who become absolutely apoplectic about FDA practices are the patient groups, because they understand exactly the cost of delay. The most famous instance involves the case of Abigail's Alliance.[10] Abigail Burroughs tried to get the use of Erbitux - now on the market - and they delayed. And they hemmed and they hawed giving her a special permission to use it and it arrived the day she died, at age 21. Not a nice situation. Erbitux is now on the market. So these error costs are very high; yet the clinical trials are not nearly as "scientific" as one would want them to be, and the raw data from the actual use, properly interpreted, is an enormous benefit and the FDA just doesn't look at it in the same way

10. Abigail Alliance For Better Access v. Von Eschenbach, 495 F.3d 695 (D.C. Cir. 2007), *reversing*, Abigail Alliance v. Von Eschenbach, 445 F.3d 470 (D.C. Cir. 2006).

as the NCCN. So be careful to laud the FDA for all its supposed expertise. Often times, the FDA is worse than worthless. It is dangerous.

RA:

I don't agree with most of that. The FDA has announced very sensibly that to let a drug on the market we need double-blind, randomized, controlled trials because that is the best kind of framework to evaluate whether a drug is safe and effective. That being said, we do have a rich resource of observational data once a drug goes on the market both in other countries and in this country, and the FDA could be doing a better job of policing post-market use. It isn't in large part because it lacks funding for post-market regulation. As part of the 2007 FDA amendments, pharmaceutical companies demanded that the user fees they pay only go to fund pre-market regulation. The FDA isn't doing enough to police drugs that are on the market by looking at what's actually happening with patients, what kind of outcomes occur in practice, and how much drugs are being used off-label.

As for requiring pre-market studies on subpopulations, that is done for a very good reason. Thalidomide is an example. If you don't test a drug in a pregnant population then you really don't how it will affect pregnant patients. Children and elderly people have different metabolic reactions to drugs, and so you can't take a drug that was approved for an adult and give it to a child and expect it to have the same sort of outcome. If we are going to use these drugs in different populations, as we should, then we need more inclusive studies. With regards to drugs that treat orphan diseases - rare diseases where you don't have a lot of potential research subjects - the FDA is flexible about required patient numbers as long as the research can demonstrate the drug is safe and effective. There are a number of mechanisms in place to speed the approval process, and researchers don't need to recruit all of their patients on the same day. Researchers can do a longitudinal study where they look at patients over the course of years, and patients are recruited as they become available.

Every country has its own regulatory framework for dealing with these issues, and that has value to us in terms of looking for best practices. Some foreign agencies are at times stricter than the FDA, like the European Medicines Agency, and some are less strict. Also, there is valuable data from these other countries from observational research and clinical trials that we should use in our own post market surveillance.

RE:

Look, the whole system turns on two questions. The first is whether the FDA lets a drug on the market. The second is whether the physician and patient decide to use it. One of the things to remember is that many drugs have received FDA approval only to just bomb when they hit the marketplace. Why is that? Because clinical judgment and collective professional wisdom, which says that yes, this drug is now legal, but it is not suitable for my patient. The amount of physician judgment after a drug is approved that occurs downstream is enormous.

Furthermore, there is nothing about that kind of information that Ryan talked about which is exclusive to the FDA. Even I know that children have different metabolic reactions than adults. So does every practicing physician. So does every expertise group. So it's quite clear that you have to be cautious about the inferences that are going to be made from clinical trials. But it doesn't follow from that proposition that the FDA is the only organization to draw those inferences. Think of a physician who has tried three recognized drugs for treatment all of cancer for a sick patient, of which have been nonresponsive. The question is, do you try an off-label drug or just let your patient die. One of the things that the FDA does is that it always uses the wrong measure of decisions. It asks – "is the drug safe and effective?" That's not the correct test. The correct test is always – "is the expected value of this particular use for this particular patient positive or negative?" And there are many cases where that balance is overwhelmingly positive and yet the drug flunks the FDA standard of approval.

DP:

You're suggesting that we should change the framework under which the FDA would operate. Change the standard that they are applying. Ryan, what would be wrong with that?

RA:

The idea that physicians can just decide on basis of their professional expertise whether a patient should be getting a drug isn't a very good argument. The reason the FDA requires pediatric studies is so that a physician can look at a pediatric study and say, "should I be giving this to a kid? Here is scientific evidence predicting how a child will respond." Instead of, "well, you know, I think I'll give them half a pill and we'll see what happens." That is not a good way to practice medicine. So while it is expensive and burdensome to do these studies, they are critical for physicians to practice medicine scientifically.

It is always a risk/benefit determination; it is never just a question of safety. That's because all drugs are dangerous, and they only become safe if there is evidence that a drug is more likely to be help than to harm. If it was just a question of whether a drug was safe, everyone could go out and take any approved drug, and you wouldn't need physician gatekeepers. Unless you're a pure libertarian, in which case you believe patients should be able to take whatever they choose. But that's why we have physicians and the FDA to act as gatekeepers.

Richard mentioned Abigail's Alliance, which was a very sad case of a young girl who died and was not able to get a treatment that was eventually approved. But that is one example out of millions of patients, and it is far more likely that the drug she wanted would not have done well in clinical trials, and that it would not have been helpful, although in this case it was. But it's not a question of her taking a drug because she's got nothing to lose. It's a question of her taking a drug that is potentially very toxic and could shorten her life, and reduce her quality of life for the time she has remaining. Before clinical trial results are known, the information does not exist for patients to make informed decisions. That's why we have to do clinical studies before we permit access.

RE:

The problem with that approach is that the physician and patient have to decide what to do now, knowing that it will take another five years to run this clinical trial. It makes no sense to wait for better information if the patient is not going to live more than 90 days unless the physician does something now. The idea that physicians have to put everything on hold when they have information that's better than random is a terrible mistake. Under these circumstances, the question that a physician faces is, "I know that this proposed treatment is very risky, but I also know what the alternatives are, and they are worse." And remember every approved drug only gets prescribed after a downstream judgment by a physician that it is appropriate for use. There is nobody - even in a libertarian world - who thinks that patients are going to self-medicate with respect to advanced cancer treatments. Abigail was in the care of the best physicians at Johns Hopkins Hospital, all of whom said she should receive this drug. They knew what they were talking about. Abigail Alliance is an organization that has recommended a number of drugs for approval. It has a 100% hit rate. Every drug it has recommended has eventually been approved, including Erbitux. This is not just talking about one case. It is talking about one tragic death that got publicity and got Frank Burroughs so mad that he formed his alliance. If you just take the number of people who die of given conditions

per year, figure out what the delays are, you're going to come up with hundreds of lost years of lives from delayed approvals.

Remember these clinical studies, after they are successfully completed are "authoritative," only in a limited fashion. They may be both approved and flawed. Or they may work for aggregates but not individual cases. Or they could fail overall but work well for a small portion of the population. Any mention of a drug cost/benefit study has to take into account the high variance in the responsiveness across a large population. It may well be that a drug flunks a clinical trial could work for some subpopulation. Letting it on the market then allows physicians to figure out whether given patients may benefit from this treatment. If the profile is wrong, don't use it. But if a patient's condition is susceptible to the drug—do use it. The FDA can't take into account the variance under a clinical trial. They only do on-off judgments, and physicians are always doing incremental judgments. The FDA is essentially, methodologically so primitive in how it thinks about medicine that it ought not to be allowed to operate under its current framework.

RA:

Partially as a result of the Abigail's case, the FDA now operates a "Compassionate Use" program, which allows patients to get unapproved drugs in certain circumstances for life threatening illnesses. But we should be very careful about giving these drugs to patients because they are more likely to be harmful than not, until proven otherwise. You have to be very careful about looking at this in hindsight bias. It's easy to look at a patient who died and a drug that was eventually approved and say, "oh well, we should have just approved that drug right off the bat, what did we even do a clinical trial for? Everyone knew it was OK." Well, no, they really didn't. They didn't know until the clinical trial data came out. It ignores the value of clinical trials, and also, the fact that we need to do clinical trials to know whether drugs are safe and effective. That's a reason to get patients engaged in clinical trials and participate in research that benefits everyone.

Clinical trials are not perfect, but they are the best possible system physicians have come up with to evaluate drugs. The issue of variance you raise argues for testing more subpopulations of patients to see if maybe this is good somewhere, and it gets back to the Thalidomide argument. If you give thalidomide to everyone you might find that it helps with Hanson's Disease, which is leprosy. You might also find that you've got 10,000 severe birth defects because everyone is trying the drug and we're seeing what happens. Again, that is not a good system.

RE:

Nobody advocates that you should take a drug and administer it to pregnant women without some kind of subtest. That is basically saying that nobody learned that point generally. But they have. When you start to figure out what's going on today, everybody understands that, and in fact there are many drugs that are licensed and they are not licensed for pregnant women and then what happens is that many physicians do the following: "I know there is a serious risk here, but the alternative is worse. So I'm going to make the off-label decision to use this on a pregnant women given the knowledge that you have." The FDA can only work with aggregates. Physicians can work with individual patients. And it turns out the downstream data is almost always better than the clinical trials. Most of which have very serious methodological limitations associated with their operations. You want to say, "oh, we'll just test it on another subpopulation," but it may take you years to accumulate enough data to see whether it works on that particular subgroup. Why on earth do you want to wait?

I'm not trying to ban clinical trials, in fact one of the things you say in favor of markets is that often times these drugs, like dealing with cholesterol and so forth, you can get very large populations and very good data from clinical trials that the drugs don't work and you take them off the market. But they would be off the market even if you didn't have an FDA. Nobody wants to go forward to a group of users, like the HMOs, and say, "well we have this drug and we're going to conceal from you all the adverse data, and by the way it isn't effective but pay us 3 billion dollars for it anyhow." Every single major buyer of drugs runs its own independent efficacy studies with respect to its own subject population and it does not rely on the FDA data, which is too gross and too unrefined for their purposes.

DP:

Let me ask you both to talk about how this downstream data can be marshaled in a world in where communication is now so easy. Assembling of databases is now so much easier than it would have been in a different era.

RE:

Well it's not through the FDA because when you report to the FDA they send you a huge investigative form, which could take hours to fill out and can subject you to potential liability. So you go through the NCCN and they get it. You have to understand, by the way, just to make this very clear

- NCCN standards are in fact used for insurance purposes for coverage. So off-label uses are covered, and it's used as the standard of care in medical malpractice cases. Unlike the FDA, which cannot collect this data because physicians just will not report to it. Nobody trusts them because you know that you reported it and then they may spend ten of your hours cross-examining you as to why you used it in the first place. It's a terribly counter productive system.

RA:

I definitely disagree with that and I think the FDA is the most appropriate party to do this. First, because when a drug manufacturer becomes aware of side effects, and doctors and patients do let drug manufactures know about side effects, the company has a statutory duty to report it to the FDA. The FDA has a very doctor friendly website that I have used, the "Adverse Event Reporting System." It is online and you can go on and fill out a patient adverse event. Yes, it takes a little bit of time, but you know we're doctors to help people. Second, the FDA has access to things that NCCN doesn't. They have access to clinical trial data. They have access to overseas databases from foreign regulatory agencies. They have access to data from the Centers for Medicare and Medicaid Services. They have access to private insurer databases. Part of the problem is that this data is fragmented. I disagree with the claim that every private payer is running its own efficacy studies, but a number of private payers do conduct research on their own proprietary data. In the case of Vioxx, for example, long before it was pulled from the market, the VA and Kaiser and other insurers pulled the drugs from their formularies or restricted access to it. Part of the problem right now is that everyone is doing that in isolation and really we should be looking collectively at all of this information. We need a way to get all of the information assembled to have the FDA evaluating it. Also, we need to incentivize third parties to evaluate it. My last paper argued that the FDA ought to be collecting and disseminating this information in a de-identified way and that we ought to create a bounty system for third parties to evaluate this data. When they produce evidence that a drug is not safe or effective there should be a payment from the government or from another party to incentivize the private industry to get involved in this whole process. Really, it doesn't need to be one or the other - we can have great private voluntary organizations doing this sort of research *and* the FDA.

RE:

All you need to do in this case is have the FDA turn its data over to the private organizations. There are trade secret issues, but they will do a better job evaluating it. I remember at least one case I worked on where the biostatisticians on the private side were so much more sophisticated than the scientists working on the government side that it was an embarrassment to see what happened when the government decided that a clinical trial that had one bad arm was to be killed off after you had spent 320 million dollars, when there were in fact statistical techniques available to save the trial. I think that if people actually work with the FDA's staggering incompetence of most of its high bound bureaucratic type figures, is something which is very large. I agree with you. I'd love to assemble databases - there are trade secret issues and all the rest of that stuff - but I would much rather them be evaluated by a private organization with professional physicians working on a voluntary basis than by the FDA, which simply is so worried about letting drugs onto the market with adverse effects.

Let me just mention Vioxx for a second. You know this was a drug, which was over promoted by Merck. I think that's fairly clear - I've seen the ads. I was frankly horrified because Merck is generally regarded as one of the best companies out there. But when you actually saw the case data on Vioxx and the litigation stuff two things happened. One, a lot of the claims for damages were completely fraudulent. People who had not even taken tablets were claiming side effects. The famous case in Angleton, Texas was a case of improper testimony on critical fact issues.[11] Remember this about Vioxx: for treating bleeding in operational settings, that is in operating rooms, post-surgery, it is still the best drug available. When you take it off the market – it's one thing to say that a manufacturer can't sell it to consumers – it's another thing to say that you can't use it in hospitals. The FDA essentially did an unnecessarily broad kind of prohibition, perhaps because it was afraid that some of this product might leak out into the general market. They did not handle the Vioxx situation at all well. The truth about the matter is, as I recall, one person saying to me, "the issue is whether you can return your Vioxx to get your money back. What you did was you found patients for whom it was successful hoarding the drug and trying to get other supplies even though it was off market." There is a lot of upstream information learned by downstream use: patients with chronic

11. Richard A. Epstein, *Ambush in Angleton*, WALL ST. J., Aug. 22, 2005, available at http://online.wsj.com/article/0,,SB112467524766419308,00.html.

disease are tremendously knowledgeable and that information is completely shut out of the FDA process.

II. AUDIENCE QUESTION AND ANSWER PORTION

DP:

Let me suggest with about 20 min remaining that we begin to take questions from the audience.

Question #1:

My recollection of the Thalidomide problem was that you had a drug that had been approved by the FDA and that it was only when the effects of drugs began to appear in a lot of babies that had been delivered out in the real world, that the doctors made the discovery of the harmful effects and notified the FDA, rather than being something that was the result of some predetermined scientific study. I wonder if this doesn't go to the costs that we tend to ignore of the whole regulatory process.

Once we get insured, and maybe overly insured, we become a little less careful about how we behave. We get a false sense of security in our actions, and it does increase injury. I wonder if that isn't one of the problems with having government regulation. When any product, and doesn't have to be a drug, it can be food, or when we go back to the origins of the FDA - you find that part of the reason was that the food industry was the one that invented the food and drug act. They wanted the government imprimatur on their products so that people in society would have a sense of security that this is really good, healthy food. Don't we run into that problem?

RE:

Yes, by the way the FDA in 1906 did not have any power to review any drugs for safety or for efficacy. It was only an agency that could prevent the shipment and interstate commerce of those drugs that were made that were not pure, so it was the Pure Food and Drug act. The only control that it had over manufacturers before the 1937 constitutional revolution was with respect to drugs that were made in territory. The 1938 statutory regime allowed oversight, but that did not require a drug to go through the FDA in all cases. Instead, if the FDA wanted to review a drug, it could call it in for some kinds of trials. The level of new drugs coming into the market at that period was vastly greater than it's been in the post period. Yes, it's been a problem. If the FDA approves it, then we do not worry about it. I don't think it's that serious today because everybody in

this business understands that given variations in patient behavior and given the difference in combinations of drugs that physicians have to be careful and watch patients individually. So I don't think physician care is the major problem. I think the delay and the heterogeneity issues are much more important.

RA:

It's been a little while since I've reviewed Thalidomide but my recollection is that the FDA kept it from coming on the market and that has been one of their great successes. In fact, the person who kept it from coming on the market, Frances Kelsey, received the President's Award for Distinguished Federal Civilian Service.

As to whether we are complacent because the FDA has approved a medicine - I don't know if the answer is to pull FDA regulation so that we are less confident that our drugs are safe and effective. I think it's better to have some drug evaluation rather than none, and that, eliminating the FDA entirely would not be good for public health.

Question #2

I want to make a comment and ask a question. I am a practicing physician and intensivist. I have a master's in clinical research, and in my experience, I have yet to come across a physician who has not been funded by a pharmaceutical company that disagrees with Professor Abbott. Not everyone in the medical community has a consensus that the FDA is doing a good job in terms of preventing some of these things from happening. In terms of Abigail's situation: she had end stage cancer, and I don't think that medication would have had a meaningful impact. It probably would have increased her life expectancy a few months in the ICU and that's it. But it's presented as if it could have saved this girl's life when that's not the case. It's a question of, are we going to sacrifice public safety over these drug. As you said, most doctors in an academic center have the ability to go ahead and use them off-label, it's just a matter of whether pharmaceutical companies should be promoting them.

My question is, I don't have any problem with non-governmental regulation, but if FDA is not going to do what it does now, how are you going to protect public health?

RE

Let me just ask the question the other way around. Right now in the oncology area we know that somewhere around 50 or 70 or 80 or 90% of

uses are off label – would you stop it all? No? Well, that's what I'm arguing for. And the question is, then how do you want to fine-tune? We've already accepted the proposition, I think incorrectly, that promotion by drug companies is improper. So what we have is the regime that you want. There is no improvement that you can make of this regime.

Now, let me say something about academic medicine, where my views are somewhat different from your own. I think like academic lawyers, we tend to believe in regulations through the Bar Association because we're cartel makers. I think there is a lot of that attitude alive and well on the medicine side. Let's us experts have a guaranteed source of income from controlling the products that make it to market. The rationalization for that conclusion is that no outsider knows enough to question the establishment. But were you to ask the same question to professional people in statistics and economics, they might have a very different view of the efficacy of the preapproval process. If you read somebody like my University of Chicago friend Tomas Philipson, who has spent his entire life as a professional economist, he expresses serious doubts about the fundamental choices on clinical trials and related issues that take place inside the medical profession. All too often the FDA relies on validation techniques that adapt too slowly in response to technological changes.

So what I would say is this, I am not against clinical trials. In fact when there are easy things to measure like, let's say, cholesterol levels with standard drugs for an aging population, clinical trials makes sense. It is easier enough to enroll sufficient numbers in trials and easy enough to do controlled tests to measure dose/response ratios. But in a lot of cases, the FDA and the drug companies don't have that luxury. To use the same model without regard to all of the differences in the available data is to me a serious mistake.

RA

That question was more directed to Richard as to what he would replace FDA regulation with . . .

RE:

Nothing.

RA:

Nothing. But correct me if I'm wrong, you have in the past suggested that the FDA should just be a certifying agency after Phase I trials, after which voluntary organizations should take over . . .

RE:
If this were a different debate, that's a harder debate to win . . .

RA:
Alright, alright, I won't get into that.

RE:
But this is about off-label use, and the cases are overwhelmingly strong. The other case is much more controversial.

Question #3

My question is, how come both of you can't come to the middle in some ways? Outside the FDAs control, let the private organizations make it a little faster, try to save money.

RA
So you're asking why we can't both just get along?

Both of our positions are on a spectrum. I think that Professor Epstein is pretty far on one end of the spectrum and I'm more on the medical orthodoxy end of the spectrum, but there are people on either end of us and in between. You could totally revamp the FDA's authority and have a much more stronger system of regulation, or some people have even argued we should get rid of the FDA altogether. Or, you can find a happy medium between the two. But for all the reasons we discussed we aren't moving towards the middle - but maybe you have.

RE
We should talk about the issue on the table not the general FDA. The reason one basically accepts them, even as a libertarian, is that Phase I trials are relatively cheap to conduct. They are kind of a public good. These trials give lots of good information, and when they turn out to be negative there is no dispute with respect to the conclusions. If you give a Phase I trial that kills five persons for every one that it saves, no physician exercising powers over prescriptions will recommend them. But the further you go down the trial path with Stage II and Stage III trials, it costs more money to produce less reliable information. The cost benefit lines cross.

At that point, try certification, which says, "hey, here's a group that thinks that this product is okay." But the key reason why the FDA-types hate certification is that anybody can do it. So anyone can turn to the von Mises Society if it sets up a drug certification program, organized by card-

carrying libertarians. Then we could get Public Citizen to run its own program. In fact, Public Citizen does run its own type of evaluation system.[12] Generally speaking, I think they are too negative and they tend not to be widely followed, but in 1971 they actually hit a home run in the case of contaminated intravenous fluids, from which dozens died and hundreds were injured.[13] So sure, certification has a huge advantage. But certification is not exclusion. And remember this about the exclusion power: if the FDA keeps the drug off the market, there is no downstream person that can correct its mistakes, if mistakes they be. If the FDA lets a drug on the market patients, patient groups, physicians, physician groups can neutralize that decision by not using it. The fact that many drugs fail suggests that downstream review is serious, because the needed information is so important. Lives are at stake.

Let me just make one point: the typical, good, cancer drug today is a six month to a nine month improvement, particularly with 2nd and 3rd stage cancers. I was at a private session about two years with Jim Watson, the surviving DNA man, and he said emphatically, "the problem with you doctors is that every one of the drugs you have stinks!" I said, "you want to kick all of the stinky drugs off the market?" He didn't want to go that far, but there is no question that cancer research needs another generation of improvement. But you are not going to get that improvement in a world in which that new generation will find it hard to get its idiosyncratic products through the FDA.

DP:
We have one more question.

Question #4:

Since the 1990s we've seen the danger of deregulation, it seems you want to put more power in the hands of private corporations. . .

RE:
Which deregulation are you talking about?

12. *See Worst Pills, Best Pills*, PUBLIC CITIZEN, http://www.worstpills.org (last visited Sept. 9, 2014).

13. *Stepping Aside But Not Out: Well-Known Consumer Health Advocate Dr. Sidney Wolfe Hands over Reins to Deputy*, PUBLIC CITIZEN (June 3, 2013), http://www.citizen.org/pressroom/pressroomredirect.cfm?ID=3903.

Audience Member:

I mean from the energy sector to banking, I mean. . .

RE:

Let me answer this question the best I can. With energy regulation, the picture is completely mixed There is no question in my mind that the heavy regulation of the nuclear power industry has forced off market a source of environmental improvements by making the industry no longer economically viable. Fracking to me is something, which has proven to be of enormous advantage under state regulation. More generally, every single price regulation for energy, e.g., gas at the pump, makes little or no sense. Many of the limits on extraction are overly restrictive. The major driver for improvement is technology, which can lower pollution per unit of production. But it is hard to generalize across regulatory programs.

The financial sector is very different. I work in that area, where the run on the bank threat is a serious challenge for which deregulatory solutions do not entirely work. I recall a time when Lawrence Summers – no slouch— thought that counterparties provided sufficient security against excessive risk. But many others who worked in the industry though that the "herd" problem can lead to death spirals and the like. It is not easy to come up with a solution, but certainly thinking about minimum capital requirements may make more sense for banks than microscopic management tests under Dodd-Frank. I don't know any serious market economist who thinks that deregulation pure and simple for banking and other financial markets is an automatic first, best solution. What the best solutions are is generally contestable.

More generally, we must remain aware of the fact that as the law moves from area to area, the externality problems, the coordination problems, the information problems, are likely to differ. So too should your regulatory response. I don't do health care exclusively; in fact, I spend most of my time on other regulatory systems. Each of them in their own way is as complicated as health system.

DP

I want to take this opportunity to thank both of our debaters.