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STIFLING NEW CURES: The True Cost of Lengthy Clinical Drug Trials

Avik S. A. Roy
Senior Fellow
Manhattan Institute for Policy Research

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Executive Summary

Though the United States urgently needs new treatments for common illnesses such as heart disease, stroke, and diabetes, the nation's system for drug approval discourages innovation and investment, especially for our most pressing public health challenges. In this paper, we find that the main culprit is the high cost of Phase III clinical trials, which are required for FDA approval of most drugs. We examined drug development in four major public health areas and discovered that for any given drug on the market, typically *90 percent or more* of that drug's development costs are incurred in Phase III trials. These costs have skyrocketed in recent years, exacerbating an already serious problem.

The enormous cost and risk of Phase III trials create incentives for researchers and investors to avoid work on medications for the chronic conditions and illnesses that pose the greatest threat to Americans, in terms of health spending and in terms of the number of people affected. This avoidance, in turn, harms overall U.S. health outcomes and drives up the cost of health care.

In this paper, we examined drug development in three such areas: obesity, adult-onset diabetes, and cardiovascular disease. We also examined the less burdensome regulatory situation in drugs for rare diseases, as an opportunity for contrast. We find that the current Phase III trial system forces pharmaceutical and biotechnology companies to take enormous financial risks and burdens them with needless and unpredictable regulatory delays. The current system has, in particular, prevented start-up biotech companies, mostly based in the United States, from challenging the dominance of large, multinational pharmaceutical concerns. It also, perversely, encourages more innovation in drugs for very rare diseases than it does in drugs for common conditions that afflict hundreds of millions of Americans.

As a result of our analysis, we recommend replacing the current "all or nothing" FDA approval system with one that reflects the realities of scientific research and the profiles of chronic long-term conditions. Such a reform would allow drugs that have been found safe and promising (in Phase I and Phase II clinical trials) to win approval for limited marketing to patients. This would give patients early access to innovative new therapies, while the FDA would retain the ability to collect information confirming the drugs' safety and effectiveness and to revoke a drug's marketing authorization later, when appropriate.

While the FDA currently has the legal power to create its own conditional approval process, it has little political latitude to do so. For this reason, we believe that Congress must create clear standards for such a pathway. Congressional action would allow regulators and companies to develop new tools that are better suited to the realities of modern drug development.

About the Author

AVIK S. A. ROY is a Manhattan Institute senior fellow with the Center for Medical Progress. His research interests include Medicare, Medicaid, the Affordable Care Act, and consumer-driven health care. He is author of The Apothecary, the influential Forbes blog on health care policy and entitlement reform. He writes regularly for Forbes.com and National Review Online, and his work has also appeared in *National Affairs*, *USA Today*, *The Atlantic*, and other publications. Roy is also the founder of Roy Healthcare Research, an investment research firm in New York. Previously, he served as an analyst and portfolio manager at J.P. Morgan, Bain Capital, and other firms. He attended the Massachusetts Institute of Technology, where he studied molecular biology, and the Yale University School of Medicine.

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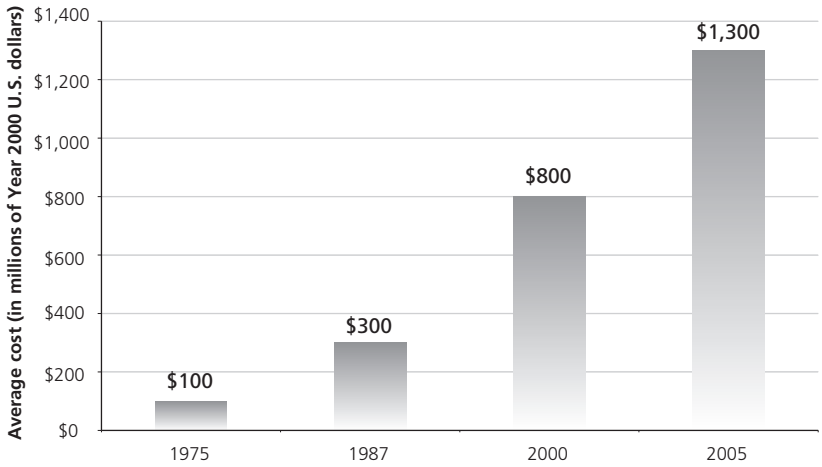
PART I: PHASE III TRIALS ARE DRIVING RISING COSTS IN MEDICAL INNOVATION

In 1975, the pharmaceuticals industry spent the equivalent of $100 million in today's dollars for research and development of the average drug approved by the U.S. Food and Drug Administration, according to the Tufts Center for the Study of Drug Development. By 1987, that figure had tripled, to $300 million. By 2005, this figure had more than quadrupled, to $1.3 billion.

The true amount that companies spend per drug approved is almost certainly even larger today. Matthew Herper of *Forbes* recently totaled R&D spending from the 12 leading pharmaceutical companies from 1997 to 2011, and found that they had spent $802 billion to gain approval for just 139 drugs: a staggering $5.8 billion per drug.

Figure I. Average Cost to Develop One New Drug



Source: Tufts Center for the Study of Drug Development

Table I. Changes in Clinical Trials: Resources, Length, and Participation			
Function	**1999**	**2005**	**Percent Change**
Median procedures per trial protocol (e.g., blood work, routine exams, x-rays, etc.)	96	158	65%
Average clinical trial staff work burden, work-effort units	21	35	67%
Average length of clinical trial, days	460	780	70%
Clinical trial participant enrollment rate (% of volunteers meeting trial criteria)	75%	59%	-21%
Clinical trial participant retention rate (% of participants completing trial)	69%	48%	-30%
Source: Tufts Center for the Study of Drug Development, Impact Report 10, No. 1 (2008)			

The biggest driver of this phenomenal increase has been the regulatory process governing Phase III clinical trials of new pharmaceuticals on human volunteers. One reason: Phase III clinical trials have become far larger and more complex than they were in the past. From 1999 to 2005, as the Tufts group has shown, the average length of a clinical trial increased by 70 percent; the average number of routine procedures per trial increased by 65 percent; and the average clinical trial staff work burden increased by 67 percent. On top of that, increasingly stringent enrollment criteria and trial protocols resulted in 21 percent fewer volunteers being admitted into trials and 30 percent more enrollees dropping out before completion of the tests.

Overall, Phase III trials now represent about 40 percent of pharmaceutical companies' R&D expenditures. But this often-cited statistic actually understates the gravity of the burden. This is because overall R&D expenditures include all pharmaceutical candidates that a company tests—including hundreds that never reach the Phase III trial stage. When we confined our analysis to those drugs that actually get approved, we found that Phase III clinical trials typically represent *90 percent or more* of the cost of developing an individual drug all the way from laboratory to pharmacy.

In this paper, we look at four particular areas of public health concern: obesity; diabetes; stroke and heart ailments; and "orphan diseases" (ailments that afflict very small populations and hence lack the normal market incentives to develop treatments). We analyzed the progress of 12 major new pharmaceuticals developed across these four categories and found that in nearly every case, Phase III trials represented at least 90 percent of the entire cost of a drug's development.

Table 2. R&D by Function, PhRMA Member Companies, 2009			
Function	**Dollars (xMM)**	**Share of Total**	**Probability of FDA Approval**
Prehuman/preclinical	$11,717.4	28.6%	8%
Phase I	$ 3,752.9	9.2%	21%
Phase II	$ 7,123.7	17.4%	28%
Phase III	**$16,300.1**	**39.8%**	**58%**
Approval	$ 2,046.9	5.0%	90%
Total R&D up to FDA approval	**$40,941.0**	**100.0%**	
Phase IV	$ 5,302.7	13.0%	
Uncategorized	$ 197.8	0.5%	
Source: PhRMA Annual Member Survey, 2011; DiMasi et al., J Health Econ 22(2003):151–85			

This cost burden creates a system of perverse incentives for researchers and industry, which discourages the rational allocation of resources for drug development. After all, only one in 12 drugs that enter human clinical trials end up gaining approval from the FDA. This risk profile has led smaller companies to go bankrupt when they have faced setbacks in clinical studies. Many private investors are withdrawing venture capital support for start-up drug companies, fearing that their investments will vanish if there is the slightest hiccup in the development process.

The consequences for Americans are higher-than-necessary health spending and poorer health outcomes. Pharmaceutical companies charge more for their products, in order to recoup their costly and risky investments. And fewer beneficial drugs reach doctors and patients.

What Is a Phase III Trial?

Federal law requires that medications proposed for human use go through "adequate and well-conducted clinical trials." Around this statutory language, regulations and standardized practices have built a three-phase system for any compound that, having emerged from basic research and animal testing, is deemed a candidate for pharmaceutical use. These three stages (paid for, of course, by the medicine's developer) begin with Phase I trials, involving perhaps 100 people at most, to assess the proposed drug's safety and whether it works in treating a particular condition, symptom, or illness. If the medication "passes" these tests, it moves on to Phase II trials, which assess how well the drug works as well as how safe it is, and they involve a larger number of people (100–300).

Only after these stages does a drug candidate move on to Phase III trials, which test the drug against placebos, as well as currently available treatments, on thousands of people. The large sample size is essential to uncovering potential side effects that may affect small percentages of people and therefore may be missed in the smaller trials. Large-scale trials also protect against statistical accidents that often occur in small samples and thus provide a more complete and reliable portrait of the drug's benefits and risks.

The importance of Phase III trials stems from the statutory language in the Federal Food, Drug, and Cosmetic (FD&C) Act. Under Section 505(d) of the act, sponsors of new drug applications must demonstrate "substantial evidence" of the drug's clinical benefit, with "substantial evidence" being defined as "adequate and well-controlled investigations … by [qualified] experts."

Under the FD&C Act, the FDA has considerable discretion to determine what constitutes "substantial evidence." The agency has interpreted the plural form of the word "investigation" in the statute to mean that companies must sponsor at least two such studies, and those studies are usually large, multiyear Phase III trials—the ones that swallow up so much private capital. By tradition, each of these trials is expected to show, with 95 percent statistical certainty, that a drug meets its tested aims of clinical benefit.

Phase III Trials Are the Biggest Driver of the Rising Cost of Innovation

In order to more accurately estimate the contribution of Phase III studies to the cost of drug development, we reviewed public filings and records for companies developing medicines in four areas: GLP-1 inhibitors for diabetes; factor Xa inhibitors for cardiovascular disease; several new drugs for reducing obesity; and medications for several rare disorders such as Hodgkin's lymphoma.

We calculated the number of patients studied in every clinical trial that the selected companies sponsored. We then cross-referenced these data with the average per-patient cost of clinical trials, as reported by a 2011 survey by the medical management consulting firm Cutting Edge Information. These are the data that show that, in most cases, companies spent more than 90 percent of their development money per drug on Phase III clinical trials. In the field of obesity,

the average was 91 percent; in diabetes, it was 93 percent; in cardiology, it was 94 percent. Only among rare disorders were there exceptions to the general rule because in that field, some companies can take advantage of the FDA's accelerated approval process and forgo Phase III studies.

Obesity

Approximately one-third of U.S. adults are obese, a number that is growing every year. Obesity is a direct cause of numerous chronic illnesses, such as diabetes, heart disease, and some cancers. Small wonder, then, that enterprising young biotech companies are attempting to develop drugs to address obesity. Yet the current regulatory framework makes their quest exceptionally, and unnecessarily, difficult.

One such company is Arena Pharmaceuticals of San Diego. Arena spent hundreds of millions of dollars developing a weight-loss drug called Lorqess, which could help lower obese patients' weight, beyond what they could achieve with conventional methods such as diet and exercise. In ten clinical trials that studied nearly 9,000 patients (and cost hundreds of millions of dollars), Arena demonstrated that its drug did get patients to achieve greater weight loss than did patients on a placebo. In one trial, 23 percent of patients taking ten milligrams of Lorqess twice daily lost 10 percent of their body weight; in the placebo arm of the study, only 10 percent of patients achieved that result.

Impressively, the drug had side effects that were almost indistinguishable from those of the placebo—a remarkably clean result. Hence in 2010, it appeared that Arena might be on its way to gaining approval for Lorqess, and helping millions of Americans reduce their risk of chronic illness.

But the FDA didn't agree. Instead, the agency held that the company had not ruled out the possibility that the drug could cause heart-valve disease. That response effectively forced Arena Pharmaceuticals to "disprove a negative" by a statistical standard that the FDA itself has called "arbitrary." Furthermore, the FDA raised concerns that the drug had caused cancer in rats years earlier, when it was in animal testing—even though no signs of cancer risk were found in the human clinical trials.

As a result of these objections, the FDA rejected Lorqess in October 2010, sending Arena back to the drawing board. Arena's stock price declined by 80 percent on the news.

Arena wasn't the only obesity-drug company to be blocked after promising trial results. Days after rejecting Lorqess, the agency (which has not approved any weight-control drugs in over a decade) turned back another antiobesity drug, Vivus Incorporated's Qnexa. Shortly after that decision, in February 2011, the FDA rejected another drug, Orexigen's Contrave, demanding that the company conduct a long-term study to prove that the drug doesn't increase a patient's risk of heart attack.

All told, the three companies had enrolled more than 18,000 patients in clinical trials costing over $800 million and achieved, effectively, nothing. "The clear lesson," wrote Matthew Herper in *Forbes* last year, "is that weight-loss medicines simply do not have enough benefit to justify any risk…. [T]hese failures will keep drug companies from investing in new obesity research [and that] will probably mean years, if not decades, before another weight-loss drug makes it to market."

Congress, struck by this tale of frustration and futility, stepped in to moderate the regulators. Last September, the Senate Appropriations Committee stated that it "is concerned with the absence of novel medicines to treat obesity, the second leading cause of preventable deaths in the United States and a disease linked to cancer, high blood pressure, heart disease, diabetes, and stroke. With only diet, exercise, and gastric surgery as options, the lack of obesity medications is a significant unmet medical need." The committee

Table 3. Estimated clinical trial expenditures for recent obesity drugs								
	No. of Patients				Est. Costs ($MM)			
	Lorqess	Qnexa	Contrave	Total	Lorqess	Qnexa	Contrave	Total
Phase I	104	0	0	104	$2.3	$0.0	$0.0	$2.3
Phase II	1,065	200	657	1,922	$38.4	$7.2	$23.7	$69.3
Phase III	7,794	3,754	4,534	16,082	$368.7	$177.6	$214.5	$760.8
Total	8,963	3,954	5,191	18,108	$409.4	$184.8	$238.2	$832.4
	Percent of Total							
	Lorqess	Qnexa	Contrave	Average	Wt. Avg.			
Phase I	1%	0%	0%	0%	0%			
Phase II	9%	4%	10%	8%	8%			
Phase III	90%	96%	90%	92%	91%			
Total	100%	100%	100%	100%	100%			

Source: Arena, Orexigen, Vivus SEC filings; Cutting Edge Information

went on to direct the FDA to report to the Senate by March 30, 2012, on "the steps it will take to support the development of new treatments for obesity."

The FDA responded to this feedback by meaningfully moderating its requirements for Orexigen's new heart-attack study. In addition, after Vivus's Qnexa demonstrated positive results in its new safety study, an FDA advisory panel of outside experts strongly recommended that the agency approve the drug, increasing the likelihood that Qnexa will reach the market. The fate of Arena's Lorqess is less clear. In each case, the additional trials will cost over $100 million.

Diabetes

Glucagon-like peptide 1 inhibitors (GLP-1 inhibitors) are considered by many endocrinologists to be the most promising new class of diabetes drugs. Amylin Pharmaceuticals and its partner, Eli Lilly, developed the first approved GLP-1 inhibitor, Byetta, along with a long-acting version of the same drug, called Bydureon. Despite clinical trials involving thousands of patients, suggesting that Bydureon is safe and effective, along with the fact that Byetta was already approved, the FDA rejected Bydureon in 2010, approving it only in early 2012 after the companies

Table 4. Estimated clinical trial expenditures for GLP-1 analogues in diabetes										
	No. of Patients					Est. Costs ($MM)				
	Byetta	Bydureon	Victoza	Taspo.	Total	Byetta	Bydureon	Victoza	Taspo.	Total
Phase I	48	12	20	18	98	$1.1	$0.3	$0.4	$0.4	$2.1
Phase II	246	105	774	490	1,615	$8.9	$3.8	$27.9	$17.7	$58.3
Phase III	1,447	3,223	4,455	6,662	15,787	$68.5	$152.5	$210.8	$315.2	$746.9
Total	1,741	3,340	5,249	7,170	17,500	$78.4	$156.5	$239.1	$333.2	$807.3
	Percent of Total									
	Byetta	Bydureon	Victoza	Taspo.	Average	Wt. Avg.				
Phase I	1%	0%	0%	0%	0%	0%				
Phase II	11%	2%	12%	5%	8%	7%				
Phase III	87%	97%	88%	95%	92%	93%				
Total	100%	100%	100%	100%	100%	100%				

Source: Amylin, Novo Nordisk, Ipsen, Roche SEC filings, FDA documents; Cutting Edge Information

supplied additional data proving that Bydureon was not likely to increase the risks of cancer and heart disease. Novo Nordisk's Victoza was similarly delayed by the FDA. The fate of Taspoglutide, a GLP-1 inhibitor from Ipsen and Roche, was even more discouraging: because Phase III trials are the only accepted way for an experimental drug to be tested on large numbers of people, the company had no way to know that Taspoglutide would prove to be less effective than already available pharmaceuticals. When Phase III trials showed that to be the case, the company lost its entire investment in the diabetes field.

Heart Disease

Factor Xa inhibitors are poised to revolutionize the way we treat a number of serious cardiovascular diseases that affect tens of millions of Americans: acute coronary syndrome, atrial fibrillation, and venous thrombosis. A striking fact about the two most advanced factor Xa inhibitors—Xarelto (from Bayer and Johnson & Johnson) and Eliquis (from Bristol-Myers Squibb and Pfizer)—is the sheer number of patients whom these companies studied, nearly all in Phase III clinical trials: more than 130,000, at an estimated cost of over $6 billion. Some 94 percent of the costs involved were, again, incurred in Phase III trials. The record for this class of drugs amply illustrates why no small company can undertake this kind of research, despite its considerable medical value. Instead, smaller firms (most often in the biotechnology industry) are forced to partner with giant companies, which have the deep pockets to assume the immense cost and risk of a Phase III trial. Hence, regulations and their consequences suit the interests of risk-averse regulators, and limit drug development to a few large companies. But the system shuts out new participants and discourages innovation.

One such example is betrixaban, a factor Xa inhibitor invented by Portola Pharmaceuticals, a small, privately held biotech firm in South San Francisco. In 2009, Portola licensed the rights for betrixaban to pharmaceutical giant Merck for an initial fee of $50 million. However, despite positive Phase II results, Merck gave up on the drug in 2011 and returned it to Portola, because the high cost of Phase III studies in such a competitive area presented even Merck with an unfavorable risk-benefit profile. Portola has stated that it will attempt to carry the drug into Phase III trials itself, though it is unclear whether it will receive sufficient funding.

Orphan Diseases

Because most small biotechnology companies are shut out of large potential markets for widespread

Table 5. Estimated clinical trial expenditures for factor Xa inhibitors in cardiovascular indications

	No. of Patients			Est. Costs ($MM)		
	Xarelto	**Eliquis**	**Total**	**Xarelto**	**Eliquis**	**Total**
Phase I	52	114	166	$1.1	$2.5	$3.6
Phase II	5,755	3,824	9,579	$207.6	$137.9	$345.5
Phase III	60,598	60,083	120,681	$2,866.8	$2,842.5	$5,709.3
Total	66,405	64,021	130,426	$3,075.6	$2,982.9	$6,058.4
	Percent of Total					
	Xarelto	**Eliquis**	**Average**	**Wt. Avg.**		
Phase I	0%	0%	0%	0%		
Phase II	7%	5%	6%	6%		
Phase III	93%	95%	94%	94%		
Total	100%	100%	100%	100%		

Source: Bayer, Bristol-Myers Squibb SEC & FDA filings; Cutting Edge Information

Table 6. Estimated clinical trial expenditures for recent drugs in selected rare diseases								
	No. of Patients				Est. Costs ($MM)			
	Soliris	Gattex	Adcetris	Total	Soliris	Gattex	Adcetris	Total
Phase I	11	8	45	64	$0.2	$0.2	$1.0	$1.4
Phase II	11	16	102	129	$0.4	$0.6	$3.7	$4.7
Phase III	184	169	0	353	$8.7	$8.0	$0.0	$16.7
Total	206	193	147	546	$9.3	$8.7	$4.7	$22.8
	Percent of Total							
	Soliris	Gattex	Adcetris	Average	Wt. Avg.			
Phase I	3%	2%	21%	9%	6%			
Phase II	4%	7%	79%	30%	20%			
Phase III	93%	91%	0%	62%	73%			
Total	100%	100%	100%	100%	100%			

Source: Alexion, NPS SEC filings; NIH; Cutting Edge Information

conditions such as stroke or diabetes, many focus instead on rare "orphan" diseases, where Phase III rules allow for smaller trials and, thus, lower costs. For example, in 2006 Alexion Pharmaceuticals gained approval for Soliris, used for paroxysmal nocturnal hemoglobinuria, a blood disease so rare that it affects only about 4,000 Americans. Prior to approval, Alexion studied Soliris on slightly more than 200 patients. Today, Soliris achieves annual sales of about $800 million, and Alexion has a market capitalization of over $14 billion. Similarly, NPS Pharmaceuticals is developing Gattex for parenteral nutrition-dependent short bowel syndrome, which affects 10,000 to 15,000 Americans. While NPS has engaged in a broad clinical program for Gattex, the company has only had to study about 200 patients for its short bowel syndrome application.

Though costs are more manageable for drug development in these rare disorders, we found that Phase III trials for "orphan diseases" often nevertheless represent over 90 percent of development costs. There is one exception to the rule: oncology. There, FDA procedures have allowed many drugs (for example, Adcetris from Seattle Genetics, for Hodgkin's lymphoma) to win accelerated approval after Phase II studies.

PART 2: IMPLICATIONS FOR INDUSTRY AND GOVERNMENT

The French economist Frédéric Bastiat wrote in 1850 of "that which is seen, and that which is not seen." Truer words could not be penned of the pharmaceuticals industry, whose great tragedy stems from that which is not seen: promising drugs that are not being prescribed because of the expense and risk of developing them.

When promising treatments are kept off the market, the patients who fail to benefit go unseen. This is especially true with common conditions such as obesity, where effective drugs would be used by millions of Americans. What is "seen," by contrast, are concerns about drugs that were approved by the agency and later turned out to pose problems. When this happens, FDA officials are often hauled before Congress and asked to defend their decisions. At the agency, expeditious approval of innovative drugs is risky; excessive caution is not.

Hence, while it is important to encourage the FDA to streamline its regulatory process, it is even more important to consider ways that Congress can create the legal incentives for the FDA to approve more pharmaceuticals and permit more companies to enter the market.

Specifically, three aspects of the agency's current approach are out of date and create significant costs and delays in the development of useful drugs.

First, the system is oriented toward acute diseases, like contagious infections, in which symptoms appear rapidly and the effect of medication is also relatively quick. Such diseases were the most prevalent menace to public health when the federal government began regulating drugs in 1906. Today, however, the greatest dangers to long-term public health are chronic non-communicable diseases such as heart ailments, diabetes, stroke, and cancer. These conditions can persist for decades. That makes it more difficult to measure the true effects of a medication in the time scale of even the most wide-ranging of clinical trials.

Second, the current approval system for a drug is "all or nothing": if a medication is approved, it is judged effective for all patients at all times, and it may be marketed by all legal means. If, on the other hand, the drug is judged not effective enough to justify approval, it is withheld altogether from the public. Yet most victims of chronic illnesses have more than one medical problem, and their symptoms vary individually over time. Medication to treat heart disease, then, may be useful in some instances, for some people, in a way that is hard to capture by an either/or evaluation method.

Third, as we have documented in this paper, the current system is extremely costly to implement. This is due not only to its very high standard of proof for effectiveness but also to the FDA's broad powers to determine what constitutes a satisfactory trial. Even after Phase I, II, and III trials are complete, the agency can, for example, demand answers to new questions or impose new criteria for success. As a result, a great deal of uncertainty hangs over even the most promising trial results.

More Balanced, More Effective: Expanding the Role of Conditional Drug Approvals

There is one step that government and industry can take to reduce dramatically the risks and cost of drug development: abandon the current black-or-white approval process in favor of an incremental, *conditional* one. In such a process, drugs could be provisionally approved after promising early-stage data, with the FDA retaining the option to revoke that approval later on, should unexpected data come to light.

A "conditional approval" approach would grant limited marketing authorization to new drugs after successful Phase II trials. Under conditional approval, patients most in need can benefit from a new drug, and companies can generate a modest amount of revenue that can help fund Phase III trials for full approval. A conditional approval for betrixaban, for example, would allow Portola to generate incremental revenues that could fund its Phase III program, dramatically reducing the risk that the company would lose everything if betrixaban failed to show a benefit in larger trials.

As we've mentioned, a conditional approval model already exists, in the FDA's *accelerated approval* process. The accelerated approval process was instituted in 1992, after a decade of advocacy by HIV/AIDS patients. Because it often takes years for drugs to demonstrate definitive clinical benefit in traditional Phase III trials, the FDA created the process to approve a drug after Phase II studies if those studies show that it is "reasonably likely to predict a real clinical benefit." For example, a cancer drug that causes tumors to shrink is "reasonably likely" to extend life. However, drugs can cause tumor shrinkage in a matter of months, whereas it may take years for a drug to definitively prove that it extends life relative to the old standard of care.

Unfortunately, the FDA severely restricts the accelerated approval process to serious, life-threatening diseases. Doctors and biopharmaceutical developers have long sought a broad expansion of the accelerated approval process. For example, Susan Desmond-Hellman, chancellor of the University of California at San Francisco, recently proposed a system in which companies could gain conditional approval in

exchange for agreeing to a more restrictive marketing authorization. She specifically cited the experience of Arena's Lorqess in her remarks:

> You could have an approval process that started out with a low-level approval. You don't get a sales force, you can't promote that drug and you can't put TV ads on it. But you could sell it. Then you increase your confidence. "We haven't seen any heart attacks after five years—looking good. The ten pounds [of weight loss] is really holding up and in fact, some of the patients as they stay on the drug longer, lost 15 pounds. OK, maybe you can have a sales force. Still no ads on TV." Then you gain more confidence; it gets to be eight years.
>
> Is there a system where we could, as we increase our confidence in safety and advocacy, allow for broader distribution and more promotion? Not a yes or a no answer? I think that could really change two things. One is, the odds in the business model would be more stacked in favor of investing in difficult things like obesity, type 2 diabetes, [and] high blood pressure, which were at risk for no innovations.

An alternative approach would be to give companies the regular amount of leeway in the way they market conditionally approved drugs but require that any promotion include information that the drug had been only conditionally approved. The drug's sponsors would face strict, contractual requirements requiring them to conduct well-controlled Phase III trials even as they marketed their pharmaceutical. The FDA could revoke a drug's approval status if those trials were not satisfactory or, if in use, the drugs ended up proving to have an unfavorable risk-benefit profile.

How Reform Would Change Development Incentives for the Better

It's worth considering how a conditional approval process could transform the economics of pharmaceutical innovation. Today, GLP-1 analogues achieve nearly $2 billion in annual sales per drug, and analysts project similar sales for approved antiobesity drugs. Using those figures, we modeled the impact of an FDA policy that offered conditional approval to such pharmaceuticals, restricting their use to the 10 percent of obese or diabetic patients whose conditions were most serious and most resistant to existing therapies. Selling to only 10 percent of a drug's $2 billion market would yield a $200 million opportunity—not too far from the average cost of Phase III trials for antiobesity ($254 million) and GLP-1 ($187 million) drugs. In other words, a conditional approval approach would let companies largely recoup the costs of later Phase III trials.

Allowing these companies to gain revenues for their medicines in these severely obese or diabetic patients would allow them to fund Phase III trials with dramatically lower financial risk, while still demonstrating that their drugs were sufficiently safe and effective. (As we've mentioned, the costs of Phase I and II trials are far lower: we estimate that obesity companies spent an average of $24 million per drug on Phase I and II trials, and developers of GLP-1 analogues have spent an average of $15 million.) Companies could engage in research for new medicines. They would still be risking tens of millions of dollars in R&D spending. But they would not be risking hundreds of millions and their corporate lives.

Worth the Effort: The Impact of Reform on Public Health and Economic Growth

Reforms to address the cost of Phase III trials have no obvious constituency in industry or government. The FDA is averse to all risk, even when there are countervailing benefits. And large pharmaceutical companies benefit when smaller players are forced to partner with the giants in order to survive the Phase III process. The general public, though, has a strong interest in repairing a system that stifles medical innovation.

The social and economic benefits of pharmaceutical innovation are plain in health statistics. For example,

between 1999 and 2005, the introduction of new heart drugs correlated with a 45 percent drop in coronary-artery disease patients dying of heart attacks in hospitals. Similarly, between 1995 and 1997, as new anti-HIV drugs became available, the annual death rate from HIV declined by 63 percent. The United States continues to lead the world in this important area, directly employing 655,000 Americans in the drug-development sector and supporting the employment of millions more.

Yet the industry faces significant danger. As described above, the costs and risks of new drug development are skyrocketing, making it more difficult to attract capital to start new biotech companies and raising questions about the ability of even large companies to sustain high levels of investment in drug research and development.

The biopharmaceuticals industry is a significant contributor to American R&D spending. From 2000 to 2007, drug companies spent $105,428 in R&D per employee, far more than any other American manufacturing industry. (Far behind, in second place, was the communications equipment industry, at $62,995 per employee.) For its contributions to the nation's economic health, to say nothing of its literal health, this industry should be encouraged to continue innovating. Unfortunately, current regulatory practices have the opposite effect.

CONCLUSION

Our research has established that Phase III trials are, by far, the biggest expense, and the biggest risk, of new drug development. In fact, we have found that Phase III trials are even more expensive than is commonly thought. That expense distorts the drug-development system so that it does not efficiently and rationally allocate time and money to find new medications. Regulators block useful drugs from reaching patients. Researchers are discouraged from attempting to serve the most numerous populations of patients. And investors face the prospect of spending vast sums for nothing.

Hence, it is of paramount importance to mitigate the binary, yes-or-no nature of drug development. This black-or-white regulatory process discourages investment in new medicines. In contrast, if the United States adopted a flexible, conditional approval approach that allowed sponsors to recoup some of their R&D costs before, or during, large-scale clinical trials, we could dramatically lower the risk and cost of

Figure 2. R&D Expenditures per Employee, by Manufacturing Subsector and Industry, 2000-2007

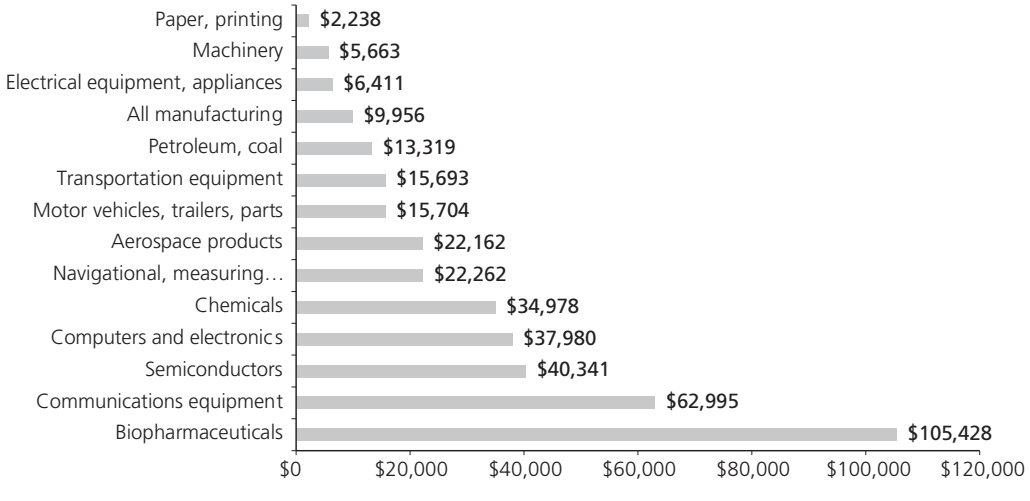


Table 7. Medicines in Development by Therapeutic Category, 2010 vs. Annual U.S. Deaths, 2009			
Disease Area	**Drugs in Development**	**U.S. Deaths, 2009**	**Drugs in Development per 10,000 Deaths**
Cardiovascular disorders	237	779,367	3.0
Lung cancer	120	158,105	7.6
Parkinson's disease	25	20,552	12.2
Alzheimer's and other dementias	98	78,889	12.4
Cancer (all subtypes)	**878**	**568,668**	**15.4**
Colorectal cancer	82	52,462	15.6
Respiratory disorders	334	137,345	24.3
Diabetes mellitus	193	68,504	28.2
Breast cancer	**125**	**41,115**	**30.4**
Leukemia	**119**	**22,697**	**52.4**
HIV/AIDS	**81**	**9,424**	**86.0**
Skin cancer	**86**	**9,254**	**92.9**
Source: PhRMA, Centers for Disease Control			

drug development. We believe that the consequence would be an explosion of private investment in medical research and development, providing a substantial boost to one of the largest sectors of our economy.

Congress, therefore, should create clear standards for conditional approvals and also give the FDA more flexibility to develop new regulatory tools that are better adapted to the rapid advances in basic science and that have the potential to accelerate patient access to safer and more effective therapies.

Along these lines, Senator Kay Hagan (D-N.C.) has introduced a bill titled "Transforming the Regulatory Environment to Accelerate Access to Treatments," or TREAT. A draft version of this bill, encouragingly, sought to facilitate the "progressive and exceptional approval" of new drugs "to accelerate patient access to new medical treatments." These include treatments that address a previously untreated disease; those aimed at patients who are failing existing therapies; and those that show unusual clinical promise.

Unfortunately, the FDA and other stakeholders opposed this measure, and it was taken out of the bill before its introduction. Instead, the current version of the proposed TREAT Act includes a modest expansion of the existing accelerated approval process—far short of what is needed to address the problem described in this paper.

The true policy solution is already clear, thanks to two decades of experience with the existing accelerated approval process. Today, the FDA's incentives impel it to avoid the "seen" error of approving new medicines that later pose concern. By contrast, it has little incentive to avoid the "unseen" error of blocking new medicines that could ease the suffering of millions of people. Only Congress can correct this distorted incentive system, by granting the FDA the authority it needs to change.

PROJECT FDA

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Utilizing 21st Century technologies to help develop better FDA regulations and a faster and safer drug and medical-device pipeline

Project FDA is a Manhattan Institute initiative which aims to reform the FDA to meet 21st century challenges. Under the leadership of former FDA commissioner Dr. Andrew von Eschenbach, Project FDA promotes reforms that can enable the FDA to offer a more predictable, transparent, and efficient pathway for bringing safe and effective new products to patients.

Medicine is on the cusp of a radical transformation. New sciences and technologies are poised to allow physicians to personalize treatment for every cancer patient; arrest or prevent the development of Alzheimer's disease; and radically lower health care costs by reducing the prevalence of expensive chronic diseases. Unfortunately, today's FDA—simultaneously overtasked and underfunded by Congress—has struggled to adapt its regulations to new scientific advances.

Project FDA believes the FDA can become a bridge for innovation, rather than a barrier to it, and that this can be achieved without sacrificing patient safety. For instance, advances in molecular medicine that allow companies to target specific sub-groups of patients, combined with electronic health records, should allow the FDA to streamline and improve time-consuming and expensive pre-market product testing that can take a decade or more, and implement vigorous post-market surveillance of "real world" patients after drugs or devices demonstrate safety and efficacy in early testing. This approach will not only accelerate access to innovative products, it should enhance efforts to safeguard public health.

Project FDA will educate the public on the FDA's vital role in advancing medical innovation; highlight the potential for new sciences to improve health while also lowering costs; and collaborate with patients groups, industry stakeholders, and policymakers to modernize the FDA's policies and procedures.

As part of our mission to advance public dialogue and debate about the importance of supporting medical innovation and personalized medicine, the Center for Medical Progress also hosts Medical Progress Today, a blog that provides a forum for economists, scientists, and policy experts to explore the scientific, regulatory, and market frameworks that will best support 21st century medical innovation.

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