

Medical Progress and the FDA

Our Future in the Balance



CENTER FOR MEDICAL PROGRESS
AT THE MANHATTAN INSTITUTE

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Introduction:

Alan Slobodin

Senior Oversight Counsel, House Energy and Commerce Committee

Panelists:

John Calfee

Resident Scholar, American Enterprise Institute

Joseph DiMasi

Director, Tufts University Center for the Study of Drug Development

Robert Oldham

Associate Director, Singletary Oncology Center

MR. SLOBODIN: Good morning. My name is Alan Slobodin, and I'm senior oversight counsel with the House Energy and Commerce Committee. On behalf of the committee and the chairman of the committee, Congressman Billy Tauzin, welcome to the Manhattan Institute's conference on the future of the FDA.

It is quite appropriate for the Energy and Commerce Committee to be hosting a conference of this sort, since we're the committee in the House with jurisdiction over the public health laws and we have recently been quite engaged on FDA issues in passing some bioterrorism-preparedness legislation. As part of that we also reauthorize the user fees in the FDA drug approval process, so there's obviously been a lot of discussion and a lot of focus in the committee on the FDA.

There will continue to be interest in policy issues that came out of the consideration of legislation that didn't get addressed in

those bills. These issues will deal with medical devices, the medical device approval system, whether or not there should be user fees, pediatric testing, drug advertising, and drug pricing.

In addition to what we're doing on the legislative side, we also have an oversight investigation subcommittee, and we've always had a history of doing comprehensive oversight and monitoring of the FDA and the public health laws. So this is of great interest to the committee, and I look forward to hearing the views and possible solutions that can be useful to the committee and Congress as we try to come up with ways to improve the FDA.

MR. GOLDBERG: Thank you, Alan. My name is Robert Goldberg. I am the director of the Manhattan Institute's Center for Medical Progress. Our mandate is to try to establish the value of medical progress, not only in the health care system but also in its overall contribution to America and American society. If any institution in American society plays a role in medical progress, it is the Food and Drug Administration. Whether it's a positive or a negative role is something that we may discuss here today.

Today we will hear from three people who can speak to the issues of the agency's role better than anybody that I know in the country. Before I turn the rest of the time over to them, I'll make a few introductory remarks and observations about the FDA and the state of medical progress in America, as it pertains to drug development.

Now as noted expert on pharmaceutical development, Peter Jennings, told us last Wednesday, most new drugs are simply carbon copies of the medicines that the FDA deems innovative and really cost nothing to develop, and many of the drugs that are currently on the markets aren't really breakthroughs at all. They are simply better advertised versions of drugs that were developed before or around 1989.

As purported evidence of how craven and uninventive biotech and pharmaceutical companies have become, Jennings reported that the FDA approved fewer new drugs in 2001 than it had in years past. That's something that all three of our panelists

will be able to address in some way, shape, or form, because there is a story behind the story.

There was also the claim made in a recent article that some of the newer agents for treating arthritis that have been developed since 1995 or '96 are not only less effective than agents that were developed, say, since the dawn of man (like aspirin), but they're also not as safe. The piece focused a lot on arthritis—neglecting to talk about depression, cholesterol, cancer, Alzheimer's, AIDS, multiple sclerosis, or cystic fibrosis, for example – and it pointed to drugs like Celebrex. It said that many of these drugs are only incremental improvements of drugs that were developed earlier, overlooking a study by Ray Woosley in 1992 that found that 70 percent of the drugs that the Food and Drug Administration had identified as 1C—of only marginal improvement—turned out to be the drug of choice for most physicians.

In that class of drugs, by the way, was an SSRI known as Prozac, which was considered by the FDA in 1987 as being of marginal improvement to tricyclics. We now know the rest of the story with SSRIs. And of course, the only treatment for AIDS, apart from the AZT and the protease inhibitors, was death; so much for that part of the story.

This leads me to another point. Jennings went on to allege that drug development doesn't really cost that much because these drugs are not that innovative. They're either knock-offs of what's on the market, or simply changes in the flavor or the color or the label. Which begs the question: If it's so easy and cheap to develop a new drug, then how come generic companies aren't jumping in and developing new drugs where there's higher profit margins, since all you have to do is market it?

We will discuss that issue too, since it seems as though, despite the heroic efforts of Alan and the members of the committee to reduce the cost and the time involved in developing new drugs, the cost of drug development is in fact increasing. It appears that while review times have declined somewhat in the area of biologics, it's still pretty hard and pretty expensive to develop a new drug.

Finally, not only is there a benefit to improving the process of new drug approval, but there's probably a benefit to marketing new drugs. Clearly, if people don't know about a particular drug, and the ways in which it can help them, they won't buy it. In this country, according to the National Institute of Health Care Management, there is some coarse relationship between the advertising of new drugs and increases in the use of those drugs.

So those are the areas with the biggest breakthroughs. The FDA regulates all of that. Some people want stricter regulation, and Alan's committee handles that as well.

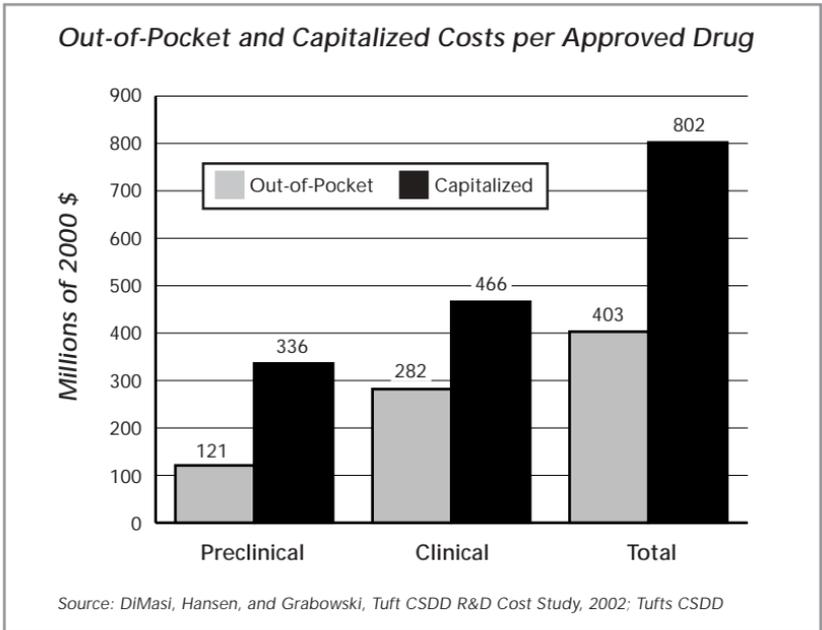
Our first speaker will be Joseph DiMasi. Joe DiMasi has been with the Tufts Center for the Study of Drug Development for well over a decade. Joe is an economist who is the leading expert on the cost of drug development and drug approval times. I'm pleased that you were able to make the trek from Boston to talk about this.

MR. DIMASI: I want to thank Bob and the Manhattan Institute for giving me the opportunity to present some of the results from our recent study on the cost of drug development. Bob has also asked me to address some criticisms of R&D cost estimates that certain activists have put out, notably Public Citizen. I think there's value in doing that, beyond merely defending my own study. It allows me to address certain aspects of the analysis that, admittedly, are probably not well understood outside of economic or financial circles.

At the outset, let me indicate what we sought to learn with our study. We were primarily interested in the research and development resource costs that have been incurred in getting new drugs from the lab to the marketplace—with particular attention to the trends in R&D costs.

We have always provided both “out-of-pocket” and so-called “capitalized cost” estimates. The out-of-pocket R&D costs are the cash outlays incurred over a lengthy development period—in this case, a 12-year timeline from discovery to regulatory approval. Capitalized cost, or opportunity cost, is the total cost that really must be considered. It accounts for what I would call the “time cost”

associated with an investment. These costs estimates also include the costs of testing drugs that fail in development. The total out-of-pocket cost is about \$400 million per approved drug, and the total capitalized cost is about \$800 million per approved drug.



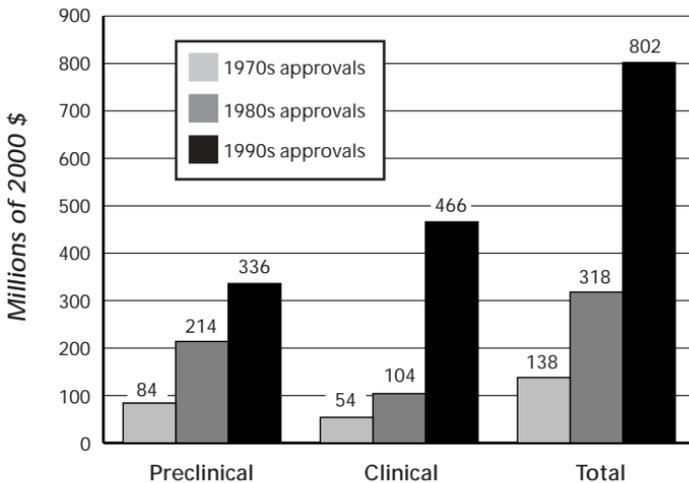
A single cost estimate by itself does not tell us all that much. It does have value when looked at in relation to the returns of that investment, or if we look at a number of estimates of costs over time—that is, if we look at trends in development costs. Significant changes over time should at least raise some flags; we can then start inquiring why the changes have occurred (though these questions may not be easy to answer). It may not be easy at all to isolate the impacts of factors that can affect costs—such as regulation, scientific advances or impediments, or even aspects of the economic environment for the products of innovation that impact strategic business decisions. But it is worth trying to understand what is driving costs.

It's also important to recognize the relationship between development costs and the extent of innovation. Specifically, less expensive development, if we can somehow achieve that, will mean that more projects will be seen by industry as worth pursuing. Thus, in the end we will likely get more therapies on the market.

We've now done three studies in our series on the cost of new drug development. They have been conducted with essentially the same methodology. That means that the results can be meaningfully compared so they can tell us something about trends in development costs. The samples for these studies cover development that yielded approvals in the 1970s, the 1980s, and the 1990s, although the data is weighted more towards the latter part of the decade for the current study than was the case for the previous studies.

Capitalized cost increased 7 percent per year between the last study and the current one. Cost increases for the clinical period were particularly high. Clinical costs increased 12 percent per year for the current study.

Trends in Fully Allocated Capitalized Costs per Approved Drug



Source: DiMasi, Hansen, and Grabowski, Tuft CSDD R&D Cost Study, 2002; Tufts CSDD

Public Citizen has tried to cast some doubt on the results and has argued that R&D costs are really much lower than what we have determined. They put out a report last summer with a very low cost estimate that was dependent on the reported out-of-pocket cost estimate from our earlier study, which was published in the *Journal of Health Economics* in 1991.

Public Citizen Cost Analyses

- *Reduce DIMasi et al. (1991) results in 2000 \$ by ignoring opportunity costs and applying the corporate income tax rate to what is left (\$110 million)*
- *Analysis using PhRIVIA data (\$71 million or \$87 million for 1994-2000 approvals)*

Source: Rx R&D Myths, Public Citizen Congress Watch, July 2001; Tufts CSDD

The number from their report released last summer that got some media attention was \$110 million—they argued that it cost “only” \$110 million in R&D to obtain FDA approval for one new drug. How did they get that number? They did just two simple things. First, they dismissed the opportunity cost notion entirely. Second, they took the reported out-of-pocket cost estimate from our previous study, updated for inflation, and then decreased that by 34 percent. They argued that you need to do so because R&D expenditures can be deducted on corporate income tax statements, and the corporate income tax rate is 34 percent.

What they’re really arguing is that government subsidizes pharmaceutical R&D through the tax to the tune of 34 percent of costs.

Public Citizen also put out a few more numbers on R&D costs that were based on trade association data on R&D expenditures and data on FDA approvals, although these numbers did not seem to get any media attention. Later in my presentation I will

show you why their use of the PhRMA data on R&D expenditures and the FDA data on approvals was inappropriate. I will also tell you how you can use them appropriately to get ballpark ranges for R&D cost estimates. We did that in our previous study and in the current one to validate our results.

Key Elements of Public Citizen R&D Cost Critique

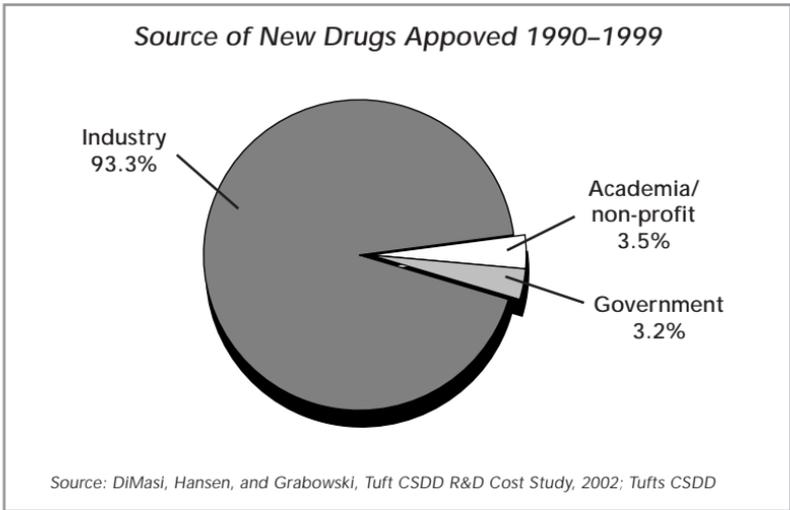
- *DiMasi et al. sample is skewed because presumption is that government pays for much, if not most, new drug development*
- *Maintains that cost estimate should be reduced by the amount deducted for the corporate income tax*
- *Opportunity cost can be ignored (“theoretical cost”)*
- *Public Citizen analysis of PhRMA data: costs are averaged over all NDA approvals (e.g., new formulations, new salts, some new uses, new manufacturer)*

Tufts CSDD

Public Citizen essentially has three critiques of our methodology. The first point is that our cost estimates are biased upward because government-developed drugs were not included. Their unsupported premise is that government finances much, if not most, drug development.

However, our sample consisted of what I refer to as “self-originated new drugs;” meaning that they are drugs that were synthesized or isolated and developed under the auspices of a single firm. It does not preclude the possibility that the firm sponsored studies that were conducted by, or in collaboration with, academics, a government agency, or a non-profit institute. It also does not preclude the possibility that the company supplied the drug to any

of these groups for their own independent investigations into the fundamental biology of disease.



My center maintains a database of drugs that have been approved in the United States through annual surveys of the drug industry. I analyzed those data and supplemented them with data in commercial databases to determine that over 93 percent of all the new drugs approved during the 1990s originated from industrial sources. Whether those drugs were self-originated or licensed-in from other firms, they were synthesized or isolated in industry.

In all likelihood, that figure—93 percent—is an underestimate of the extent to which industry finances drug development. Self-originated drugs all come from an industrial source. But self-originated drugs have somewhat lower approval rates than do licensed-in drugs. So the proportion of investigational drugs that are self-originated is actually higher than the proportion of drugs that are approved. For that reason, the share of investigational drugs that come from industrial sources should be higher than the 93 percent shown here.

Our estimates are also meant to be representative of the experience of big pharma. There was significant new entry into

the industry in the 1990s, as a number of start-ups sponsored new drug approvals. They were somewhat more dependent on non-industrial sources, primarily academia, for discoveries. Of the firms that were included in our R&D cost survey, which we believe are representative of big pharma, 98.8 percent of their approvals originated from industrial sources. So it's really hard, I think, to argue that our sample was unrepresentative, as Public Citizen does.

Public Citizen also maintained that we should take 34 percent off of an R&D cost estimate because R&D expenditures are deductible on corporate income tax statements and 34 percent is the corporate income tax rate. In essence, Public Citizen views deductions under the corporate income tax structure to be a form of corporate welfare. If the corporate income tax rate were 34 percent, they would argue that government was effectively subsidizing 34 percent of R&D costs.

Perspective on Corporate Income Tax

- *Public Citizen effectively views corporate income tax R&D deductions as corporate welfare for the pharmaceutical industry*
- *But corporate income tax meant to be a tax on profits, not a tax on sales with a special tax break for R&D costs*
- *Costs must be deducted from revenues to obtain a tax base for a profits tax*

Tufts CSDD

The major objective in our study, as I mentioned earlier, was to reliably estimate the resource costs that have been incurred in discovering and developing new drugs, and to compare them to the resource cost estimates covering earlier periods. Since tax structures change over time, resource cost shifts should be analyzed independently of taxes.

However, even if the objective is to analyze the effective cost to firms, as opposed to the cost of the resources used, Public Citizen's premise is false. It reflects a faulty understanding of the nature of the corporate income tax. The tax is intended to be a tax on corporate profits, not a sales tax. Profits are equal to revenues minus costs; deducting R&D expenditures and other costs from revenues is a means by which the base for a tax on profits can be determined. In short, subtracting the costs that generate that income from taxable income is not a tax break for corporations.

However, I should say in the interest of completeness—although this is something that Public Citizen clearly did not have in mind—that one might wonder whether there is a tax issue related to sub-optimal administration of the tax with regard to how costs are measured. Specifically, one might consider the issue of the appropriate depreciation of intangible assets like R&D. I won't go into tax esoterica here, but the potential effect would be much lower than the amount deducted. And one can reasonably argue that this is not a tax break anyway, when considering that the optimum treatment of costs is most likely not technically feasible.

You might also be wondering about the research and experimentation tax credit and the orphan drug tax credit. However, for big pharma, and our estimates relate to the development costs of big pharma firms, these credits are not sizable in relation to R&D expenditures. For example, from recent public data on a sample of large pharmaceutical firms, I estimated that these credits together amount to something in the neighborhood of 2 percent of R&D expenditures.

Again, though, our estimates were designed to look at changes over time in private sector resource costs related to new drug development, and Public Citizen's notion that cost deductions on the corporate income tax are really tax subsidies is clearly flawed thinking.

Moving on to the issue of opportunity cost, we used the cost of capital estimate for the pharmaceutical industry to determine that amount. The cost of capital was estimated from published financial data and utilized a standard finance methodology. The cost of capital is used as a sort of interest rate and applied to

Cost of Capital and Capitalization

- *Cost of capital: expected return required by investors to invest in drug development*
- *Estimated from stock market price data and debt-equity ratios for pharmaceutical firms*
- *Used as the discount (interest) rate to capitalize R&D costs to marketing approval according to development timeline*
- *Effectively captures the “time” cost of development*

Tufts CSDD

R&D costs as they occur during development. What we are really doing here is determining what I would call the “time cost” of drug development.

These time costs are real, not theoretical. The concept is quite clear. It’s not controversial at all to economists and finance professionals, but many others, I have to admit, have difficulty with it.

Let me also offer a simple example that illustrates the opportunity cost concept for the kind of application we are interested in—investment in a development project.

Suppose we have two development projects, A and B. Both projects have the same out-of-pocket costs. However, the potential returns to project A are earned immediately, while it takes ten years for investors to get any returns from project B. Rational investors will view project B as more expensive than project A.

To put things a little differently, suppose that the returns to two investments are identical. One investment project costs \$400 million out-of-pocket spent over 12 years before the returns are realized. The second investment project costs \$500 million out-of-pocket, but it is spent over nine years before its returns are realized. How do we calculate which investment is better? There is no way of knowing just from the out-of-pocket costs. We have to

Opportunity Cost for Investments

- *Consider two investment projects, A and B*
- *Both projects require the same out-of-pocket expenditure (say, \$400 million)*
- *However, returns to A are realized immediately, but investors must wait 10 years before returns to B are realized*
- *Rational investors would conclude that B is effectively much costlier than A*

Tufts CSDD

determine the time costs for the two investments. From economic and policy perspectives, it is the capitalized cost that matters.

Let me turn to Public Citizen's analysis of the PhRMA data. These are data that they make publicly available, and data they've been collecting for close to 40 years. You have to really understand

Public Citizen Analysis of PhRMA Data

- *Uses domestic or domestic + foreign (U.S. firms only) expenditures of member firms*
 - > *But what about foreign R&D of foreign firms?*
 - > *But what about R&D of nonmember firms?*
- *Denominator consists of all FDA approvals*
 - > *Appropriate treatment of R&D for already approved drugs is to obtain an estimate of post-approval R&D cost per approved drug and add it to a preapproval estimate per approved drug*

Tufts CSDD

the PhRMA data to see what is wrong here. Except for one year, PhRMA reported R&D data for the U.S. expenditures of all its member firms, and the foreign R&D expenditures only for its U.S.-owned members. Public Citizen uses these totals lagged and related to the FDA approvals of all firms.

Now much of the foreign R&D of foreign-owned firms will be related to getting drugs approved in the United States. Basic research and pre-clinical development of these firms is directed in large part, or perhaps in whole, toward finding new drugs that they hope will eventually get approved in the United States. The FDA will also look at all clinical data that are available when an NDA is submitted, regardless of the location of the trials. So you're missing a lot of the relevant expenditure data if you exclude foreign R&D.

Secondly, not all pharmaceutical firms that get approvals in the United States are members of PhRMA. This was particularly true during the 1990s; the period to which the Public Citizen data mostly applies. A significant number of approvals in the 1990s, even for traditional small molecule drugs—that is, non-biotech drugs—were obtained by firms that were not members of PhRMA. Obviously, you can be significantly underestimating the costs per approval if you have in the numerator expenditures for one set of firms, and in the denominator the approvals of a much larger set of firms.

Finally, Public Citizen uses the number of all FDA new drug application approvals from the Center for Drug Evaluation and Research, as did the recent NIHCM report that was used in the Peter Jennings special. Included in that list are a lot of applications for improvements or modifications to already-approved drugs. For example, to better serve its customers' needs, a firm might fill out its product line for a drug that was originally approved in tablet form by submitting an application for the approval of an oral solution formulation, in order to make it easier for children or adults who have trouble swallowing tablets.

Now the correct way, I believe, to deal with this sort of development is to examine the amount of R&D that is done—after the original approval of a new drug—to determine the post-approval costs for the drug. You can then add to that the pre-ap-

proval costs to get the total R&D cost for the drug. We've done that in our study. But first, let me tell you the results of an analysis that we have in our study to validate our results that used the annually published PhRMA data.

DiMasi et al. Analysis of PhRMA Data

- *Uses estimated self-originated pre-approval R&D expenditures (domestic and total foreign) in 2000 dollars by year for member firms*
- *Links R&D expenditures to self-originated approvals only for member firms*
- *Develops range based on domestic-only and domestic plus total foreign expenditures*
- *Range for out-of-pocket costs: \$354M–\$558M*
- *Range for capitalized costs: \$650M–\$1,023M*

Source: DiMasi, Hansen, and Grabowski, Tuft CSDD R&D Cost Study, 2002; Tufts CSDD

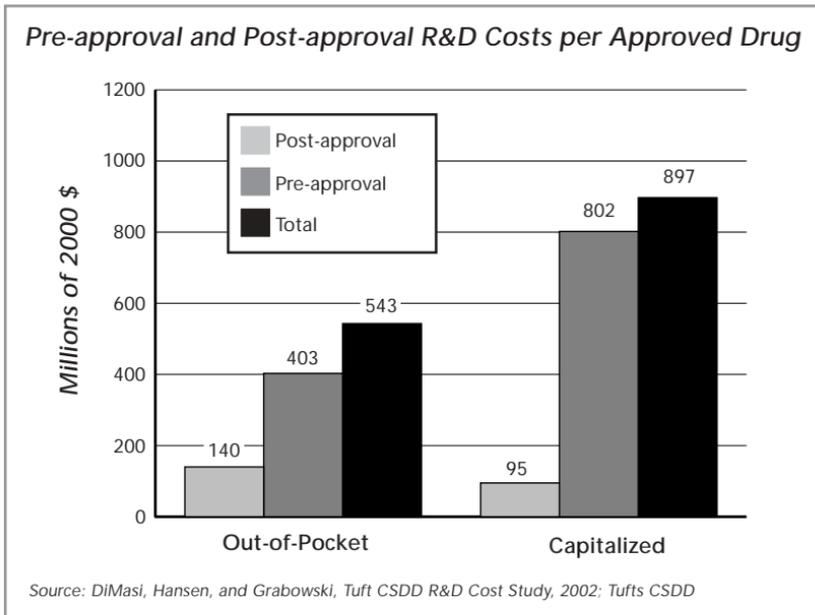
You have to work hard and be very careful to get something meaningful out of these data; they won't yield a precise estimate. All you can really get is a range within which the cost should lie. Since our sample consisted of self-originated drugs, and since a lot of the R&D expenses for licensed-in drugs will not show up in the PhRMA data because they were incurred by non-member firms, we estimated the amount of the PhRMA data that went into pre-approval work on self-originated drugs.

Then we used an appropriate lag structure to link the R&D expenditures to the self-originated new drug approvals for member firms only. Using information from the one year in which PhRMA reported all foreign R&D of all its member firms, you can get a range that at one end is based only on domestic R&D expenditures, and at the other end is based on the sum of domestic and foreign R&D.

We did that by carefully examining which firms were in PhRMA and for what periods. There was some movement in and out. The range for out-of-pocket cost was \$354 million to \$558 million; our \$403 million fits in there. As I said earlier, the true cost is probably not close to the end points, but it should lie somewhere in that range. And you can impose a lag structure and get capitalized costs that range from \$650 million to \$1 billion, and of course our \$802 million result lies within that range.

The last cost issue I want to discuss has to do with the measurement of R&D costs that are incurred after original approval and that may result in additional approvals for the same drug—that is, the same active ingredient. These approvals might be, as I mentioned earlier, for additional dosage formulations, such as an oral solution, an injectable form, or an extended release, or they might be for new uses of the already-approved drug.

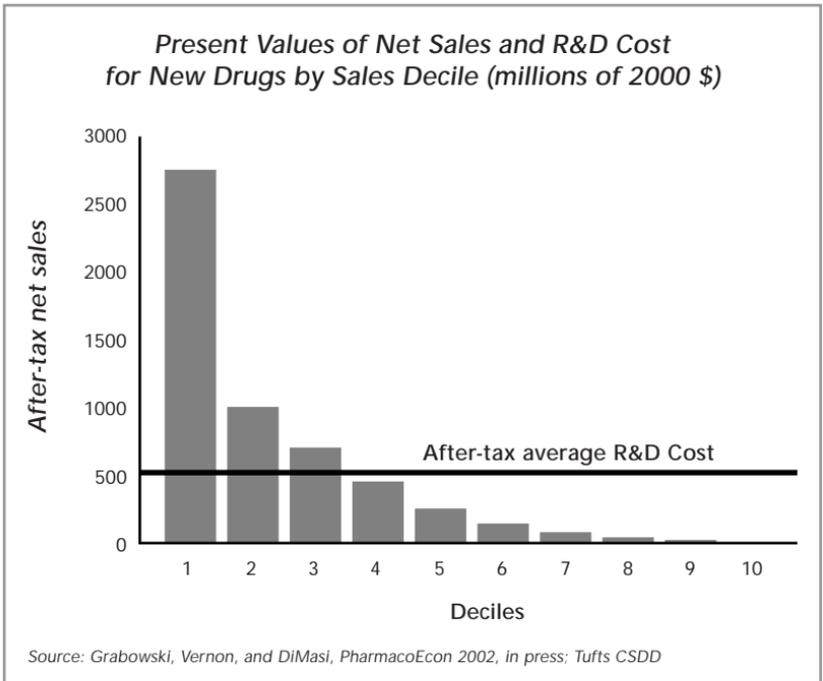
Whatever the post-original approval R&D is directed towards, it should be added to the pre-approval cost to get the total R&D expenditures per new drug—that is, per active ingredient—over



the entire development and product lifecycle. Post-approval R&D, we estimated, adds \$140 million in out-of-pocket costs and \$95 million in capitalized costs to give a total capitalized cost of about \$900 million per approved new drug.

For some policy perspectives, we need to look at costs in relation to returns. These are results from the most recent analysis of the rate of return to new drug development. Only 34 percent of new drugs earned back at least the industry average R&D cost. And the industry's cost of capital—that is, the expected return required by investors—was about equal to the rate of return for new drug development for the industry as a whole.

The results are similar to those for rate-of-return studies that covered earlier periods, including a study done by the now-defunct Office of Technology Assessment. All of this evidence suggests that the industry did not earn significant sustained excess profits.



I know that this runs counter to the popular wisdom about the profitability of the pharmaceutical industry. It's often said that the profitability of the pharmaceutical industry greatly exceeds that of other industries. The statistics on relative profitability that are the basis of these claims are annual *Fortune* magazine figures on accounting profits. But these measures give relative profit rates that should be seriously biased upward for the pharmaceutical industry. Economists have been aware of the reasons for this bias for decades.

To summarize quickly—to get some precision on R&D costs, you need to look at project-level data. The methodologically appropriate approach is to focus primarily on capitalized costs. This is particularly important for the pharmaceutical industry since development times are so long.

Our results about high costs and significant increases over time are corroborated by independently determined data that are not solely confined to the PhRMA data. There are data out there obtained independently on increases in clinical trial sizes—and in the number of procedures administered to subjects in clinical trials—that support the hypothesis that costs have risen significantly.

What we need to do now is ask why costs have increased, and consider what might be done, if anything, to reduce costs, as lower costs should induce more innovation.

MR. GOLDBERG: Thank you, Joe.

That leads to our next panelist, Bob Oldham. Bob is associate director of the Singletary Oncology Center in Thomasville, Georgia. He's clinical professor of medicine in hematology at the University of Missouri-Columbia. He was with the National Cancer Institute from 1980 to 1984 as associate director of the Division of Cancer Treatment, and he founded the program of biological-response modifiers. He is an editor of a book called *Principles of Cancer Biotherapy*, and CEO of Cancer Therapeutics, a company that is helping people develop individualized responses to their own lymphocytes.

He's going to talk about how clinical trials can be improved to reduce development times and reduce costs.

DR. OLDHAM: I want to start by talking a bit about the same thing that you just heard from Joe, and that is debunking a few generally agreed-upon principles having to do with the FDA. First, it's widely believed that the FDA is becoming more and more efficient over time, and that more new drugs are becoming available to all of us. The fact is that the number of new drugs approved per year has not changed significantly in the last decade. Between 25 and 35 drugs per year get approved, and that has not changed since 1990. So it is not true that the FDA is more efficient now than it was in terms of getting new drugs to patients in need.

It's also said that the approval time for new drugs is getting shorter. That's true because of the dataset that the FDA uses to tell you about its wonderful work. The approval time they talk about is the time from the paperwork submission for an NDA—a "new drug approval"—from the company to the time the FDA gives the go-ahead to be able to have the drug sold commercially. Indeed, that's dropped from some 30 months in the early 1990s to some 15 to 18 months today. Hence, they have shortened the time to approval and are correct in that story.

Unfortunately, the total drug development time has increased by more than half over that period of time. How has that happened? It's happened because the FDA has put in place a whole series of new rules to get the paperwork ready. The package to be submitted is bigger, it takes longer, and it costs more, so the approval time is shorter. But to us as consumers, or patients, or doctors, the actual approval time has continued to go up. So the total months-to-market rate has increased dramatically, from 120 months in 1980 to 180 months today. And the total cost of development has also increased dramatically.

What are the real issues in that increased time and cost? The answer is the FDA requirements for clinical trials. In 1980, an average of 30 clinical trials were done per NDA. Today, that average has increased to 68. The number of patients examined in clinical testing to get a new drug approved in the '80s was about 1,300 patients per drug, and today it's 5,000 patients per drug. So it is true that the FDA is approving more quickly, but it's also true that

it's taking longer and costing more because of the rules being changed in the game being played. I want to make it clear that our FDA is not more efficient, and in fact it has caused drug development to become even more laborious, even more time-consuming, and even more costly.

Now I will shift to the second part of what I'd like to talk about, and that is the drug development and approval paradigm we have today for drugs applied to large markets. Does it make any sense to apply that paradigm to what I'll call "patient-specific therapies?" Patient-specific therapies are those treatments that are originated, developed, and given to an individual patient. Let's take, as an example, the treatments for a cancer called lymphoma. I wrote an article about this in the *Wall Street Journal* in April, entitled "FDA Trials Cost Lives."

For patients, the bottom line is that they're interested in getting new treatments before they die. They cannot suffer toxicity after death—something that the FDA has had trouble recognizing. That is, they're very concerned about toxicity, but toxicity for people with one year left to live—or after death—is not an issue. So I agree with the FDA in terms of being very careful about the next Valium or the next Prozac and doing 5,000 patients per new Prozac; that's an excellent strategy. We do not want people who are not going to die tomorrow to be subjected to toxicity risk.

However, if someone only has six months to live, you need a different standard. Likewise, if you're developing a treatment for an individual human being, you can't apply the economic factors you've heard about today to that development. No one person could afford a \$300 million, \$400 million, or \$800 million development cost for a treatment; we have to have a different system there.

Lymphoma is a cancer of our lymph nodes or our lymphocytes. It turns out that each person's lymphoma is different. That might surprise you, but I don't think it would intuitively, because if you look around the room you'll notice that none of us look alike. That's because we each have a different genetic code.

Wouldn't it be bizarre if we all developed cancer tomorrow and our cancers were all alike? Intuitively, even to the non-scientist,

tist, it doesn't make any sense that all cancer is alike, or all breast cancer is the same, or all lung cancer is the same, and that we ought to develop drugs that are magical trapdoor answers to each of these problems for everybody. In fact, it's therefore obvious that since cancer arises in our own genetic code, each cancer must be inherently different in each one of us.

So as the technology of drug development comes forward, we're beginning to recognize, particularly with the code for our genes now being available, that indeed each of us is different—something that we recognize in a group such as this intuitively. If this is true, then each cancer developing in each of us must also be different.

On each cancer cell in lymphoma patients there's a little protein sticking out of the membranes called an idioType. You can isolate that and you can make a vaccine to it. But guess what? The vaccine must be different for each human being.

How are we going to take the system we're talking about today and develop vaccines for patients with lymphoma? It simply won't work. Indeed, we're already there in one sense. Seventy-five percent of all the patients treated with this idioType vaccine, as I put in my article, are in remission five years later.

So what is the logical thing to do? What would the FDA require at this point? If 75 percent of patients are in remission from a cancer five years later, what should we do? It's obvious, isn't it? We should do a randomized trial to prove that this vaccine works. That's exactly what has been initiated by the National Cancer Institute under FDA guidance: randomizing half the patients to the vaccine and giving the other half "standard" treatment, meaning chemotherapy. Then we can prove, as they say on their web site, "once for all" if a cancer vaccine works.

My thesis would be: Let's prove these treatments are safe—safe in the relative sense of cancer patients—and then let professionals do their work—that is, the doctors, cancer specialists and the people that take care of cancer patients. Let them figure out which one works the best and not subject these individual treatment modalities to efficacy standards that take thousands of patients.

In the case of this lymphoma vaccine—it will take more than five years and some 500-plus patients to prove that it really works. During that time, of course, a substantial number of people will die while the FDA is proving that this vaccine, which has three-quarters of the patients in remission five years later, really works.

A good example of this can be found with another drug, Glibac, which was just approved for chronic myeloid leukemia (CML). Glibac has had a 95 percent response rate, meaning 95 percent of the patients were better. The FDA is going, “Wow, we approved that one quickly because it’s such a good drug.”

But what did they ask for in the post-marketing period? A randomized clinical trial. They wanted to run Glibac against interferon and a chemotherapy drug—the old treatment for CML. So post-marketing they started that trial, and after only a few months they had to stop it because all of the random patients on the old treatment were doing poorly and all the Glibac patients were doing well. Any cancer specialist could have said this would happen, because it’s intuitively obvious from the information available.

I think that the government would do well to look into the change of standards that occurred in 1962, when Congress asked the FDA to begin to regulate efficacy (whereas before that time they only regulated safety). I believe that new drugs would come to the market at a much lower cost and bring opportunities to patients much more quickly if the FDA were primarily concerned with safety.

Today’s *Wall Street Journal* says the FDA is going to allow drugs with only safety tests to be given to patients in the event of a bioterrorism event. So if you get anthrax, you can get a drug that hasn’t been tested in anthrax. But of course, if you get *E. coli* sepsis, which you die from just the same way as anthrax, you can’t get such a drug; or if you have cancer, you can’t; or if you have AIDS, you can’t. This makes no sense to me at all. If we are trying to protect the population against bioterrorism by changing the standard to safety only, why shouldn’t we protect the rest of us against all the other ills of mankind that also cause lethal disease to kill us within, say, a year, for the same reasons?

I would suggest the change ought to be to something like “safety only” or “safety primarily for lethal diseases.” For diseases like cancer and AIDS, bioterrorism, and those things that we can die from quickly, we should have a different standard. Moreover, if we’re going to develop treatments for individual human beings that can’t use the market forces described in the first presentation, then we ought to have a different track to bring those drugs to market because they’re simply different animals being developed.

MR. GOLDBERG: Thank you. Jack, do you want to pick up on that?

MR. CALFEE: Dr. Oldham has certainly hit on the heart of the problem going back 40 years now. In the wake of the 1962 amendments, which did change the FDA’s mandate so that they would have to approve efficacy as well as safety, people—particularly Sam Pellsman at the University of Chicago—went back and found that there was basically very little benefit from that change in the law, but a lot of cost. Drug approvals were drastically slowed down after the 1962 amendments. There is very little evidence that there was much of a payoff in terms of getting better drugs than there were before.

I might add something else that Dr. Oldham did not mention, but that the economists have emphasized, which is the way that the FDA procedures and laws have worked out since 1962. The effect has been a fairly fundamental bias towards large pharmaceutical firms as opposed to small firms. The apparatus of getting drugs tested and approved is far more complicated and far more expensive than it used to be. To some extent the extra complexity and cost does give a payoff: After all, we know more about testing drugs now than we did before.

But nonetheless, there is a bias against smaller firms. There is an advantage to being a larger firm when you’re dealing with the FDA bureaucracy, and I think that imposes an extra cost. It has definitely slowed down the arrival of new drugs that in many cases would have been quite useful.

There are a few other points I would like to add; first focusing a little bit about the new drug approval business and then something about marketing and advertising, since that's been the topic of the day for some time at least (especially since the Peter Jennings special of last week).

A week or two ago the FDA announced that it had reached a settlement with Schering-Plough, and the dispute was over manufacturing facilities. Essentially, the FDA staff had proposed to shut down roughly 80 percent of Schering-Plough's manufacturing facilities. This would've involved manufacturing facilities that were producing drugs that were selling \$6 billion a year; hence it was fairly close to shutting down a large pharmaceutical company. Again, the dispute was over manufacturing facilities and the quality of the manufacturing.

There was a lengthy set of negotiations that took a year and a half. At the end of those negotiations, the FDA agreed that the whole thing would be settled by having Schering-Plough pay a fine of \$500 million to the FDA, and then allowing them to proceed with their manufacturing. So they did not have to shut down any of their facilities.

The remarkable thing here is that none of the drugs involved in the dispute are going to be recalled. There is no advice going out to doctors and patients that they should avoid using the drugs that were manufactured here. There appears to be no health impact whatsoever on the various problems that the FDA identified. What was really going on—and this is quite clear from the news stories—was that the FDA thought it was time to ramp up the quality and the nature of drug manufacturing, and this was a tool they were using to get this ramping up to take place.

They obviously disagreed with the industry as to whether it was worth the investment to do this. But they have prevailed and the industry is ramping up their manufacturing. And of course, it isn't just Schering-Plough; it's throughout the industry. This is a very expensive process, and there's little intuitive reason to think that we're going to get much of a payoff from it. The basic point is that the industry is doing this. It obviously has no choice; in fact,

you're hearing almost no criticism from the industry about this rather amazing development.

The next question is: Does this have any connection with new drug approvals? The answer: It certainly does. In Schering-Plough's case, it was made very clear that since the FDA had serious doubts about the ability of Schering-Plough to manufacture a drug safely, it had serious doubts as to whether Schering-Plough would be able to manufacture any new drugs that could be approved safely. The result was, as far as one can tell from press reports, that Schering-Plough's new drug approvals were largely on hold while it was resolving its manufacturing problems.

But it wasn't just Schering-Plough. Another *Wall Street Journal* story has described that Eli Lilly, which has roughly half a dozen drugs under review by the FDA, is also fighting with the FDA over manufacturing standards. In the meantime, until the fight over manufacturing is resolved, Eli Lilly's new drug approvals are largely on hold. There is definitely a linkage.

Again, we're not getting much from the industry. There's very little in the way of public complaints about this. The reason is because FDA regulation is so comprehensive that manufacturers have no choice but to maintain good relationships with the FDA staff in every respect. And on the whole, if the FDA says, "We don't want you to do this, we don't want you to do that, but we do want you to do that," manufacturers may voice their displeasure in private, but in the end they will do what the FDA asks them to do.

How is this relevant to the entire panoply of new drug approvals? I think it's very relevant because, just as the FDA has been basically ramping up its own view of what manufacturing standards ought to be, they're also ramping up their own view of what the standards ought to be for new drug approvals. Oncology drugs are a good example, not only for the rather exotic, cutting-edge kinds of therapies that are coming out of the biotech community—including Dr. Oldham's work—but also for the mainstream, traditional cancer therapies that are not biotech drugs and are not coming from large firms.

The FDA is basically moving the goalposts. They're saying, "We think that in your clinical trials, instead of proving that your drug reduces the size of tumors, we think you should also prove that when you do that you reduce mortality from the drugs." It's a very different kind of endpoint. It's a very different enterprise to prove that your drugs save lives; it obviously takes a lot longer to do that. Obviously you're going to lose many more lives along the way, if in fact your drug is effective and you have to wait until enough extra people die in the control group to prove that your new drug is superior.

That is taking place, and the reason it's taking place is because the FDA has this power to enforce its new standards on the industry. The industry has very little ability to resist. They can resist in private, but they cannot resist in public, and in the end they have to give in.

I think we need to understand that the agency now has sufficient power to do these kinds of things, more or less on its own, and it would probably be a good idea for the public to understand this process and the situation more than it does right now, because the stakes for the public are very, very high.

I think that Dr. Oldham has a good point. One doesn't have to go as far as he suggested to make progress. His point is that the FDA should be testing for safety but not for effectiveness, and he points out that how you do this varies a lot depending on the kind of drug you're testing, who's taking the drug, how many people will be taking the drug and for how long, and that kind of thing.

But I think that, in general, the problem of standards is something that goes far beyond oncology drugs. It's something that involves the way the FDA generally regulates, and it would be good if there were a lot more sunshine on the entire process. Congress could hold more hearings in which they could have people talk frankly about the FDA drug approval process, and whether or not there should be some rethinking about how the standards are being set.

That's something on the NDA business. Regarding marketing and advertising, I think that the FDA, as bad as it's been, has

actually been getting better in recent years. The medical literature tells us that there are a large number of people who are diagnosed with serious conditions—in some cases life-threatening conditions—that are not getting treated. We know this not only from individual studies but also from massive consensus reports that have been put together by the Surgeon General's Office and other organizations.

We know from experience in lots of markets that manufacturers of branded products do have an incentive to solve these information problems. They can take the information that's missing from the market, attach it to their brand, disseminate that information, and help to solve the information problems in the market. They can do something about the massive information deficits. This has happened in lots of markets, and the most common example of this that we see everyday is price advertising. There's no way people can go out and learn that much about the prices of a particular product without going to a great deal of effort. Advertising brings such information to them and makes markets far more competitive.

There are reasons to think that this same process works in connection with health care. There are also reasons to think that the same process would work in connection with pharmaceuticals. The most spectacular example of this is the direct-to-consumer (DTC) advertising that's become so prominent in recent years. The FDA has expanded the scope of DTC advertising by changing the way it interprets its regulations.

The results are now rolling in, in the form of consumer surveys and other studies, and they are looking very, very good. DTC ads are providing a lot of useful information to consumers. They tend to focus on the products that provide benefits more to consumers than they do to managed care or employers; which is good because a lot of the most important benefits of products—of drugs—ultimately do go to consumers.

In other words, the ordinary patient often has a bigger stake in using new drugs than managed care has in getting them onto new drugs. What we're finding is that that is where the DTC adver-

tising tends to focus. Consumers like the ads, which often cause them to talk to their doctors about conditions they had never previously discussed—including some very important life-threatening conditions.

When consumers are asked about how things go when they talk to their doctor about a drug they've seen advertised, the consumer says that almost every time the conversation goes very nicely. They almost never receive any resentment from their doctors in talking about advertised drugs. They are also picking up a lot of risk information about drugs from TV and from looking at the print ads—especially drugs that they are interested in. The ads appear to help quite a bit in compliance with drug therapy. They remind people to take their prescriptions, and they remind them of why they are on a particular drug therapy. That's helping to solve one of the most difficult and longstanding problems there is in medicine, which is trying to get people to comply with their medical regimes.

Consequently, when you think about all of this, it's not really surprising, although it's not well known, that several months ago the National Health Council—a large organization of the voluntary health agencies, including the American Medical Association, American Heart Association, et al.—put out its own consensus statement which said that it is very clear that the benefits of DTC advertising heavily outweigh the costs of the DTC advertising, and that DTC ads should be continued rather than restricted.

Even David Kessler—a commissioner of the FDA during the early and mid-1990s who steadfastly opposed the expansion of DTC advertising and was able to stop it from happening until he left in 1997—has now conceded that he was mistaken in his opposition. He has said, in effect, that the ads are doing much more good than harm, and that permitting these ads on a wider basis has been of distinct benefit to the consumers.



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