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FAITH SEEKING UNDERSTANDING

Big Pharma: The Truth About Drug Companies

I’ve read a book by Marcia Angell, M.D. entitled: *The Truth About the Drug Companies: How They Deceive Us and What to do About It.* Dr. Angell is a former editor in chief of The New England Journal of Medicine, so her experience adds credibility to what she says. Some of what she reports is disturbing, and I've written a few articles for the website based upon the information she reports in her book. What follows is a compilation of the previously four separate articles: Big Pharma: Its Size and Profits; Big Pharma: The Black Box of R&D Costs; Big Pharma: Innovation and "Me Too" Drugs; Big Pharma: Innovation and Research Costs.

Big Pharma: Its Size and Profits

The first issue concerns the sheer size and profitability of the pharmaceutical industry known as “big pharma.” Dr. Angell reports that prescription drug sales are over $200 billion per year in the U. S. alone. This figure refers to direct consumer purchases through drugstores and mail order pharmacies; but does not include what is spent for drugs administered in hospitals, nursing homes, or doctor’s offices. These figures are from information gathered in 2004, but they still seem to give an approximate sense of the industry’s current sales figures. IMS Health reports that U. S. retail drug sales alone for 2005 totaled 182.7 billion, a 4% increase over 2004. IMS Health is a company used by the pharmaceutical industry to monitor global pharmaceutical market intelligence.

The IMS Health global estimate for pharmaceutical sales in 2005 was $602 billion. Countries with the largest increase in pharmaceutical sales for 2005 were Brazil (38%), Mexico (16%), Canada (14%) and Argentina (13%). The sales growth of pharmaceuticals in other countries seems impressive compared to the meager 4% increase in the U.S. However, when you need to realize is that of the four countries named here, the country with the highest retail drug sales in 2005 (Canada) had only $12 billion dollars worth of retail drug sales; a mere 6.5% of the U. S. drug market. Of the countries listed in the December 2005 IMS Health sales report, Germany had the 2nd highest national pharmaceutical sales figures, at $26.7 billion; 14.7% of the U. S. market share.

Dr. Angell notes that it is virtually impossible to get precise figures on drug sales because they pass through so many hands before reaching the consumer; and they are paid for in “exceedingly complicated, often hidden ways.” You need to know whether a sales figure refers just to prescription drugs or if it includes over-the-counter drugs and other consumer products made by the drug companies. You also need to know whether the sales figure accounts for just outpatient consumer purchases or whether it includes mail order and health facility purchases as well.

The profits made by drug companies are hard to believe. In 2002, “the combined profits for the ten drug companies in the Fortune 500 ($35.9 billion) were more than the profits for all the other 490 businesses put together ($33.7 billion).” However, the drug industry justifies its high prices and profit margins by stating it needs the cash to cover the high costs for research and development (R & D) of new drugs. In 2001, the industry put these costs at $802 million for each new drug they bring to market.

The pharmaceutical industry admits that Americans pay a disproportionately larger share of this R & D because it charges Americans far more for the same drugs than it does people in other countries. Many other countries regulate their drug prices, so the drug industry argues that if Americans don’t pay these higher prices, we may wake up one morning and find that there are no more new drugs being developed. Alan Holmer, the president of PhRMA (Pharmaceutical Research and Manufacturers of America), the industry’s trade association, said:

> Believe me, if we impose price controls on the pharmaceutical industry, and if you reduce the R & D that this industry is able to provide, it’s going to harm my kids and it’s going to harm those millions of other Americans who have life-threatening conditions.

The argument is that Americans have to pay higher prices because no one else can or will pay it. Americans need to shoulder the huge investment in scientific research of new drugs for the good of humanity. Given this argument, Dr. Angell comments “that it is crucial to ask how much it costs the industry to bring a new drug to market. Is it really $802 million?” The answer to that question will be dealt with in part two of Big Pharma.

Big Pharma: The Black Box of R & D Costs

Given the justification of the pharmaceutical industry that Americans need to pay the high cost of R & D because no one else will, how much does it really cost to develop a new drug? Marcia Angell suggests that getting an answer to this question is not as easy as it sounds. While industry wide averages for total R & D are available, the pharmaceutical companies regard specifics, such as what each company spends and for what purposes, as proprietary information. Henry Waxman commented that, “The basic problem is that all pharmaceutical costs, including research, are in a black box, hidden from view.” This secrecy seems odd since the industry justifies the necessity for its high prices by its high R & D costs.

The R & D “Scare Card”

The FDA seems to agree with the $800 million R & D figure. On September 25, 2003 Dr. Mark McClellan, the newly appointed Commissioner of the FDA, gave a speech before the First International Colloquium on Generic Medicine. He remarked that “If we do not find better ways to share the burden of developing new drugs and biologics, all of us will suffer. . . . The heart of this problem is that we are not all paying our fair share of the costs of bringing new treatments to the world. And this problem is getting worse.” Dr. McClellan stated that according to some estimates, it costs more than $800 million to develop a new drug. While acknowledging that this figure has been disputed, he then stated that: “none have argued with the fact that the cost of development is large and has doubled over the past decade.”

McClellan warns that if the developers of new medical products do not have "an assurance of payment for success that reflects the value of these new treatments . . . [t]hey will not risk the high cost and the years of effort in collaboration across an increasingly broad range of scientific disciplines." Unless someone covers the cost of R & D investment, the improvements in health we've seen in recent decades will slow and stop. The United States, according to McClellan, is paying the bulk of the costs of developing new drug treatments. "But it is clear to me that we cannot carry the lion's share of this burden for much longer. And the consequences for world health will be grave, if we don't come up with a better alternative than each nation only acts with its own short-term interest in mind." For the text of McClellan's speech, go to the FDA website.

McClellan repeats the rationale of the pharmaceutical industry for why its costs to Americans are so high: Americans pay more for the same drugs than people in other countries because other countries regulate their drug prices. If the U. S. didn't charge Americans more, R & D investment for new drugs would drop, and we would face a future where new, life-saving medicines aren't being developed with the same frequency as they have been over the past several decades. And people with life-threatening conditions would die as a consequence. So it's worth the $800 million dollar R & D cost per new drug because we are saving lives, right?

Estimating R & D Costs

One way to do a very rough estimate of the R & D cost for "new drugs" by PhRMa members is by looking at the newly approved new drugs (NDAs) by the FDA over ten years (1995 through 2004) and the PhRMA data for R & D over the same time span. Looking at costs over a ten year span of time can approximate the cost of developing a new drug, as PhRMA reports that it will take 10 to 15 years of R & D to develop a new drug. Using the ten year range would then give a "high ball" estimate of those costs. Another factor indicating this as an overestimate for the R &D costs for a new drug is that for a given year, R & D costs reported by PhRMA companies would not only be for the new drugs approved by FDA for that year. Nevertheless, we can gauge an approximate, albeit, high, estimate of the R & D costs by PhRMA member companies per newly approved FDA drugs over a ten year time span. Between 1995 and 2004 the

FDA approved 934 NDAs, and PhRMA reported R &D cost of $254 billion for the same time period; for an R & D cost of $270.9 million per new drug. Subdividing the data into two five year periods, we see that between 1995 and 1999, R & D cost per new drug was 186.6 million, while from 2000 to 2004 the R & D cost per new drug was 370.7 million. While its seems that by this very rough estimate R & D costs have doubled over the past decade, it also seems that the reported R & D cost of $800 million for each new drug is high by at least a factor of two.[1]

It would seem that Dr. McClellan formed his conclusions from data gathered by sources similar to that of PhRMA (Pharmaceutical Research and Manufacturers of America). The 2006 PhRMA Profile, referencing a study done by Joseph DiMasi, an economist with the Tufts Center for the Study of Drug Development, reported that the estimated research costs for one new medicine, spread over the average development time of 10 to 15 years, was $802 million. This was an update of an analysis done by the same group over a decade ago, where the cost analysis for developing a new medicine was around $400 million. So we now see the source for McClellan's claim that research costs for developing new drugs have doubled over the past ten years from $400 million to $800 million.

Examining the Tufts Study

Marcia Angell has noted several problems with the Tufts study. First, the analysis looked at sixty-eight drugs developed at ten drug companies over ten years. However, the names of the companies and the names of the drugs were never revealed. Additionally, all the data on costs of those drugs was supplied confidentially to the Tufts group by the participating drug companies. It seems that the researchers were not able to independently verify the data; they had to take the companies' word that the data was legitimate. This is highly unusual for scientific publishing. See "The Price of Innovation: New Estimates of Drug Development Costs," by DiMasi et al, in the *Journal of Health Economics,* 2003.

A second concern is that the Tufts study was restricted to what the FDA refers to as "new molecular entities" (NMEs). These NMEs are typically only a fraction of the

[1] For further information on the numbers and kinds of drugs approved each year, see the FDA website.

number of new drug applications (NDAs) approved by the FDA each year. In 2004, the last year for which data is available, there were 113 “new drugs” approved (NDAs) by the FDA. Of that total, only 31 (27.4%) were NMEs; and of those 31 NMEs, only 17 (54.8%) were “Priority Reviews,” meaning they were considered significant improvements over already marketed products. The data for NDAs over ten years, from 1995 through 2004, indicated there were 934 new drugs approved; 305 (32.7%) of which were NMEs; and of those NMEs, only 120 (39.3% of the NMEs) were “Priority Reviews.” If we presume similar averages for the Tufts analysis, the $802 million dollar R &D figure given by DiMasi et al only applies to 32.7% of the “new drugs” approved yearly by the FDA. Yet “$800 million” is regularly cited by PhRMA, the FDA, the media, and others as the R & D cost for ***all*** new drugs. An equally disturbing implication of these extrapolations is that only 27 of the Tufts 68 NMEs were a significant improvement over already marketed products (Priority Reviews). More on this when we examine “me too” drugs in a later article.

A third problem with the $802 million dollar figure of the Tufts study is that it includes the “opportunity cost” (an accounting practice of adding theoretically lost revenue to the actual out-of-pocket R & D cost) for the 68 drugs examined. The actual out-of-pocket R & D cost reported by DiMasi et al was $403 million per drug. So the $800 million cost for developing one new medicine over 10 to 15 years, cited by Dr. McClellan (the Commissioner of the FDA in 2003) and PhRMA, should be cut in half to reflect actual out-of-pocket costs to a drug company when developing a “new drug.”

A further problem with the $802/403 million dollar figure of the Tufts study is that it is in pre-tax dollars. R & D expenses are fully tax deductible. So if we lower the out-of-pocket cost of R & D by a percentage equal the 34 percent corporate tax rate, the $403 million Tufts estimate becomes an after-tax net cost of around $266 million per “new drug.”

So the widely accepted figure of $800 million in R &D cost to develop a new drug, originally reported in the Tufts study, appears to be an inflated report of the after-tax net cost of $266 million per “new drug.” In addition, the $266 million figure can only be applied to NMEs, which I’ve projected to be about 1/3 of the total NDAs approved by the FDA in any given year. And since DiMasi et al did not independently verify the data provided by the drug companies, even this figure of $266 million is suspect. The true R & D cost for a new drug is likely to be even less than $266 million. Additional new drugs, those referred to as “me too” drugs because they are variations of older drugs already on the market, would cost even less to develop.

DiMasi et al of the Tufts Center have produced a rebuttal of the above criticisms, which were originally raised in “Rx R & D Myths,” a report by Public Citizen, a nonprofit organization representing consumer interests. See the respective websites of Public Citizen and the Tufts Center for the Study of Drug Development for pdf files of the respective papers. DiMasi et al said that “estimates in our studies were meant to examine trends in private sector resource costs.” So “opportunity costs,” reflecting the theoretically lost revenue to the actual out-of-pocket R & D cost, were legitimately included in their projected cost figure for developing new drugs. While there are additional points made within their rebuttal, the fundamental distinction between the Tufts Center notion of R & D “cost” and that of Marcia Angell and Public Citizen is evident. The Tufts Center looked at “resource costs,” of R & D while Angell and Public Citizen examined “out-of-pocket costs.” While economists may understand that the $800 million cost for developing a new drug is not the out-of-pocket cost, the average person reading in *The New Times* or on the PhRMA website about the high cost of developing a new drug will be thinking that it does reflect “out-of-pocket costs.” At the very least, unqualified use of the $800 million figure is misleading to the general public; and it is used by the pharmaceutical industry to justify its extreme profit margin and the high cost of prescription medication to Americans.

Return on R & D Investment

So what type of return can pharmaceutical companies hope to get from their R & D investments? Let’s look at retail sales data reported by the National Institute for Health Care Management Research and Educational Foundation (NIHCM Foundation), a non-profit, non-partisan group that conducts research on health care issues. The following information is for retail drug sales in 2001, the most recent data available on their website. We’ll look at the top nine selling drugs in 2001, all of which had multi-billion dollar sales figures.

Rank	Drug	Type of Drug	2001 Sales in millions
1	Lipitor	Cholesterol Reducer	4517.5
2	Prilosec	Antiulcerant	3999.0
3	Prevacid	Antiulcerant	3195.8
4	Zocor	Cholesterol Reducer	2739.2
5	Celebrex	Antiarthritic	2387.2
6	Zoloft	Antidepressant	2152.5
7	Paxil	Antidepressant	2124.1
8	Vioxx	Antiarthritic	2026.2
9	Prozac	Antidepressant	1993.8
	Fluoxetine (generic Prozac)	Antidepressant	730.6

The number one selling drug in 2001 was the cholesterol reducer, Lipitor, with $4.51 billion in retail sales. Prilosec, an antiulcerant, was 2nd with $3.99 billion; 3rd is another antiulcerant, Prevacid with $3.2 billion; 4th is Zocor, another cholesterol reducer, with $2.73 billion; Celebrex, an anitarthritic, was 5th with $2.39 billion in sales; Zoloft, an antidepressant was 6th with $2.15 billion; Paxil, another antidepressant was 7th with $2.12 billion; Vioxx, the infamous antiarthritic was 8th with $2.0 billion in sales; and Prozac, an antidepressant was 9th with $1.99 billion in sales. 2001 was the first year that generic Prozac (as Fluoxetine) was available. Using the $266 million estimate of the R & D cost of a new drug, in 2001 alone Prozac sales were 7.5 times this R & D estimate. The sales data also indicates that even in the year it lost its exclusive patent rights to Prozac, Eli Lilly and Company was able to make a profit over and above the PhRMA and Tufts Center reported cost of developing a new drug, $800 million. And Prozac has been on the American market since 1988. By 1999 retails sales of Prozac had exceeded $28 billion. It seems that if you have a multi-billion dollar sales year with a medication, you can expect a minimum return of 7.5 times the average R & D investment **per year** that you hold exclusive patent rights to the medication.

Big Pharma: Innovation and Research Costs

Americans are growing increasingly skeptical about the pharmaceutical industry's claim that drug prices need to be high to cover its R & D costs, especially the costs for developing new, innovative drugs. The evidence indicates it's not as risky for pharmaceutical companies to develop new drugs as they suggest. And even though the industry spends billions on R & D each year, the federal government and others do most of the riskiest, more costly research necessary to develop a new drug.

A Complementary Partnership

The pharmaceutical industry disagrees with this second contention. In fact, PhRMA, the Pharmaceutical Research and Manufacturers of America, challenges what they refer to as "a persistent misconception" that the National Institutes of Health (NIH) does most of the "heavy work" in discovering new medicines. "In fact, the vast majority of the medicines patients use today were developed by pharmaceutical research companies." The pharmaceutical companies are reported to spend "far more on biomedical research and development" than the NIH. This would seem to true in terms of sheer dollar amounts. In 2004, the NIH's entire budget was $27.9 billion, while PhRMA member companies spent $38 billion in new research and development. The *Pharmaceutical Industry Profile 2006* projected that R & D expenditures for PhRMA member companies in 2005 to be $39.4 billion; the estimated R & D for the entire biopharmaceutical industry was $51.3 billion. There are questions as to whether some of the industry spending is truly for "research," but for now we'll accept the reported figures as legitimate.

PhRMA said that while government and NIH-funded academic scientists "do a terrific job" advancing the basic knowledge about biology and disease, "pharmaceutical company scientists lead the way in translating basic science into practical medicines that help and heal patients." Again, in the *Pharmaceutical Industry Profile for 1996,* "the

National Institutes of Health plays a vital role in drug discovery by funding basic research into the fundamental mechanisms of disease. This allows the industry to focus on finding ways to intercept disease mechanisms."

While the NIH agrees that there is a complementary, "partnership" between the federal government and the pharmaceutical industry in developing new medicines, it does not see their role in the relationship in the same way the pharmaceutical industry does. Rather, the NIH is on the "frontline of the fight against disease," where the "cross-fertilization between public and private biomedical research" in the U.S. has made it the world leader for innovative biomedical science and technology. "The unique U.S, system of public support for science, mainly through the National Institutes of Health, is the foundation of that success."

This seems to be a version of the two blind men who describe an elephant from their respective investigation of the trunk and the tail. Both the pharmaceutical industry and the NIH acknowledge that the federal government, mostly through the NIH, does the basic research on the fundamental mechanisms of disease, which the drug industry then translates into practical medicines through applied research. The significance of its basic research is emphasized by the NIH. The importance of ongoing applied research is underscored by the pharmaceutical industry. The rhetorical difference between the two descriptions of the partnership underlies the seemingly conflicting views of what occurs.

Distorting the Difference Between Basic and Applied Research

The primary motivation of basic research is to expand human knowledge, not to create or invent something. There is generally no obvious commercial value to the discoveries that result from basic research; and this pursuit of knowledge for the sake of knowledge means that its findings are generally available to anyone, including the pharmaceutical industry. Applied research is meant to solve practical problems and to improve the human condition, rather than to acquire knowledge for knowledge's sake. One way to look at the difference between basic and applied research is to ask how long it will take before a practical application can result from the research. If a practical use cannot be envisioned in the near future, then the research can be described as basic. If a practical use is only a few years away, then the work can be defined as strictly applied research. However, if a practical use can be envisioned, but fulfillment of that vision is more than a few years off, then the research is somewhat applied and somewhat basic in nature. This third option is the case for R & D development of a new drug, where it takes an average of12 to 15 years to discover and develop a new drug.

Most countries make the results of basic research widely available at little or no cost, which means that investment in basic research can be unprofitable for private industry. Researchers or their backers often cannot receive enforceable property rights, such as patents, from basic research unless it has well-defined links with applied research. With applied research, worthwhile applications can be patented to give companies enforceable property rights to the fruits of their research—a drug, a piece of medical equipment, or a medical device. This creates strong incentives for pharmaceutical companies to invest in potential medical breakthroughs, but not necessarily in the basic research necessary to develop these breakthroughs.

Another factor that seems to play a role in the opposite-ends-of-the-elephant perspectives between the NIH and PhRMA is their primary respective audiences: U.S. citizens for the NIH and financial investors and stockholders for PhRMA. Both NIH and PhRMA want to reassure their audiences that its money was well spent.

The pharmaceutical industry seems to exploit the difference between basic and applied research, and to distort information about the R & D process for a new drug, in order to justify the high prices for its product and maintain the extreme profit margins available to it through this "partnership" with the federal government. And big Pharma has been very successful at this for over two decades. Every year since 1982 *Fortune* magazine has ranked the drug industry as the most profitable in the U.S. "During this time, the drug industry's returns on revenue (profit as a percent of sales) have averaged about three times the average for all other industries represented in the Fortune 500." Let's look at how PhRMA exploits and distorts this difference between basic and applied research.

PhRMA cites a 2001 NIH report where it says that the NIH found that only four of 47 medicines with sales of $500 million or more had "a significant government investment." But this statement is based upon the report finding that the NIH only held patent rights to four of the 47 medicines. In 2001, Congress asked the NIH to assess the return to taxpayers when a therapeutic drug, developed from technology funded by NIH, became a "blockbuster" drug and reached annual product sales of $500 million per year. To address Congress' request, the NIH analysis focused on **patent rights,** since it is only through such rights that a financial interest can be established for a product. So this finding, referenced by the pharmaceutical industry to refute the “misconception” that the government develops most of the drugs on the market, focuses on the criteria most likely to point to how pharmaceutical companies have developed the vast majority of medicines in use today: patent rights from applied research.

Several studies have shown that many important and popular drugs were developed with taxpayer support of basic research. A 1997 study by Iain Cockburn (University of British Columbia) and Rebecca Henderson (MIT) found that publicly funded research played a part in developing 14 of the 21 most important drugs introduced between 1965 and 1992. A 1998 investigation by Alice Dembner of *The Boston Globe* found that 45 of the 50 top-selling drugs from 1992-1997 received government funding for some phase of their R & D. A 2001 study by Darren Zinner published in the journal *Health Affairs* reported that for the year 1998, only 15% of the scientific articles cited in patent applications for clinical medicine came from industry sources; 54% came from academic centers, 13% from government sources, and the rest from other public and nonprofit institutions.

Willing to cite the above noted findings from a 2001 NIH report, the pharmaceutical industry has been more reluctant to communicate the findings of an earlier, unpublished report from 2000, “NIH Contributions to Pharmaceutical Development.” Obtained by the consumer watch organization, Public Citizen, the February 2000 document was a case study analysis of the top five selling drugs of 1995 (each with over $1 billion in sales), which was done to evaluate to what extent public funding of research contributed to the development of these medically and commercially successful products. It concluded that, “NIH-funded research played a critical role in drug discovery in each of these cases.” U.S. taxpayer-funded researchers conducted 55 percent of the published research projects leading to the discovery and development of these drugs, while foreign academic institutions conducted 30 percent of the published research projects. The remaining 15% of the published research was done by industry or patent-holder sponsored studies.

Researchers at U.S. universities and the NIH contributed to the R & D of these drugs by discovering basic phenomena and concepts, developing new techniques and analyses, and participating in clinical applications of the drugs. And public researchers often tackle the riskier and more costly basic research, making it easier for industry to profit. Most of the R&D spending by the drug industry occurs after companies believe they have a marketable drug. "NIH Contributions to Pharmaceutical Development" concluded: "To the extent that basic research into the underlying mechanisms of disease drive new medical advances, the R&D in industry is not performing the role played by public research funding."

The significance of the government funding for basic research also seems to outweigh the R & D conducted by the drug companies when you consider that "publicly-funded researchers have 90 Nobel Prizes compared to just four by industry scientists, although the industry spends more on R&D."

The majority of the risk and expense for basic research into what will some day become life-saving medications is done by the federal government and others; not the pharmaceutical industry. About $27.4 billion (74%) of the R & D spending by PhRMA member companies in 2004 was for applied research; not basic research.

If you have an interest in further reading on this topic, see the PhRMA web site for the report, "What Goes Into the Cost of Prescription Drugs?" and the *Pharmaceutical Industry Profile 2006.* Also, see "The Benefits of Medical Research and the Role of the NIH, May 2000;" originally available through the Joint Economic Committee at jec.senate.gov; but now available on the web site for the Medical University of Ohio at Toledo: https://www.meduohio.edu/research/nih_research_benefits.pdf.

See the Public Citizen web site for pdf files of "Rx R&D Myths" and Appendix C, which contains the unpublished February 2000 report "NIH Contributions to Pharmaceutical Development."

Big Pharma: Innovation and "Me Too" Drugs

A significant proportion of the new drugs developed by drug companies and approved by the FDA each year are simply variations of older drugs already on the market, what Marcia Angell and others refer to as "me too" or "copy cat" drugs. In 2004, 17 drugs with the "therapeutic potential" to improve on the clinical performance of drugs already on the market were approved by the FDA; the other 96 approved in 2004 were "me too" drugs.

Innovation Levels and Research Spending for New Drug Applications

The gauntlet run in developing pharmaceuticals means that for every 250 potential drug candidates examined in pre-clinical lab and animal studies, only five compounds are approved for clinical trials with humans. In order for researchers to test a drug candidate in people, they have to submit an Investigational New Drug (IND) application with the FDA, which then reviews all the findings from the laboratory and animal studies to make sure humans will not be exposed to unreasonable risks in clinical trials. Up to half of the compounds fail to make it through the clinical trials phase. If clinical trials demonstrate that the experimental medicine is both safe and effective, the drug company files a New Drug Application (NDA) with the FDA. After an extensive review, the FDA will approve or reject a drug application. About 10 to 15 percent of all NDAs are initially rejected by the FDA.

Given the above description of the approval process for a new drug, it's a reasonable assumption that by the time a drug company submits an IND application with the FDA, it has patent rights on some if not all of the important aspects of the new drug application. We've clearly entering into the applied research domain of the pharmaceutical industry. So how innovative are the drug candidates it brings to the FDA for approval? And what percentage of its R & D spending is for applied and basic research?

Research Spending

PhRMA reports that 74.1% of its R & D expenditures in 2004 ($27.4 billion) went for research after an IND was submitted, what I've suggested as the criteria for when applied research begins in most drug development. PhRMA members only spent $9.6 billion in drug discovery and pre-clinical trial research; what I've suggested as the areas for basic research. In contrast, the NIH reports it distributes 80% of its $28.9 billion in federal funding (about $23 billion) in mostly basic research grants. So at least 74% of all the R & D expenditures by PhRMA member companies in 2004 was for applied research, while about 80% of the funding for the NIH was for basic research.

Innovation Levels

Using the FDA's classification system for new drugs, the National Institute for Health Care Management Research and Educational Foundation (NIHCM) developed a continuum to assess the innovation levels of new drug applications from very innovative to slightly innovative.

When a pharmaceutical company files a NDA, the FDA classifies it in two ways. First, is whether or not the drug is a new molecular entity (NME), or a newer version of an older drug; what the NIHCM refers to as "incrementally modified drugs" (IMDs). The second way a drug is classified by the FDA is according to the "therapeutic potential" of the drug to improve on the clinical performance of drugs already on the market to treat the same condition. If the new drug has "therapeutic potential," then the FDA gives the drug more rapid attention; a priority review instead of a standard review. If the drug seems to have therapeutic qualities similar to those already on the market, even if it is a NME, it receives a standard review. The "me too" drugs would then include all IMDs (newer versions of an older drug) and the Standard Review NMEs (new molecular entities with therapeutic qualities similar to those already on the market) and the "other" category.

The NIHCM continuum of innovation is then as follows: Priority review NMEs; Standard review NMEs; Priority review IMDs; Standard review IMDs; and an "other" category which is primarily older drugs with new manufacturers. We can use this system to classify the innovativeness of the FDA's new drug applications from data obtained from their web site: www.fda.gov/cder/rdmt/pstable.htm.

New Drug Applications by Innovation Levels and Calendar Years

	1990-1994		1995-1999		2000-2004	
	#	%	#	%	#	%
Pr NMEs	63	18	71	14	49	11.5
St NMEs	63	18	114	22.5	71	16.7
Pr IMDs	28	8	42	8.3	27	6
St IMDs	128	36.6	249	49.1	247	57.8
Other	68	19.4	31	6.1	33	8
All MDAs	350	100	507	100	427	100

The analysis indicates that since 1990, the percentage of Priority NMEs, the most innovative class of drugs approved by the FDA, has decreased while the least innovative class (Standard IMDs) has increased. Priority NMEs were 18% of all NDAs approved between 1990 and 1994; and only 11.5% of all NDAs between 2000 and 2004. Standard IMDs were 36.6% of all NDAs approved between 1990 and 1994; and 57.8% of all NDAs between 2000 and 2004. Two-thirds of the new drugs approved by the FDA since 1990 have been a revised version of an older drug, and 19.3% of the NMEs approved were not an improvement over the "therapeutic potential" of drugs already on the market. Only 14.3% of the new drugs approved by the FDA between 1990 and 2004 were NMEs with the "therapeutic potential" to improve on the clinical performance of drugs already on the market! The rest were some type of "me too" drug.

How profitable are some medications? Here is an example reported by Dr. Angell on page 207 of *The Truth About Drug Companies.* In late 2003, South Africa's Competition Commission ruled that GlaxoSmithKline, the major manufacturer of AIDS drugs, has violated the country's Competition Act by charging excessively high prices and refusing to license their patents to generic manufacturers in return for reasonable royalties. Following that ruling, Glaxo agreed to permit four generic companies in South Africa to make three of its AIDS drugs and sell them in all forty-seven sub-Saharan African countries. AIDS treatment now sells for as little as $300 a year in Africa, compared with more than $10,000 in the United States.

If you have an interest in further reading on this topic, see the PhRMA web site for the report, "What Goes Into the Cost of Prescription Drugs?" and the *Pharmaceutical Industry Profile 2006.* Also, see "The Benefits of Medical Research and the Role of the NIH, May 2000;" originally available through the Joint Economic Committee at jec.senate.gov; but now available on the web site for the Medical University of Ohio at Toledo: https://www.meduohio.edu/research/nih_research_benefits.pdf. See the Public Citizen web site for pdf files of "Rx R&D Myths" and Appendix C, which contains the unpublished February 2000 report "NIH Contributions to Pharmaceutical Development."

Big Pharma: How Effective are Antidepressants and Other Drugs?

Perhaps one of the most disturbing assertions by critics of the major drug companies is how they can manipulate the FDA approval process to bring a new drug to market. Marcia Angell writes that with drug companies now involved in every detail of the clinical trial research process, there are dozens of ways for the companies to rig clinical trials and make their drugs appear to be more effective than they are.

Since 1980, drug companies have become richer, more powerful and less willing to rely upon academic researchers to test their drugs. As a result, a new industry of for–profit research companies known as contract research organizations (CROs) emerged. CROs were first organized as outsourcing companies to oversee clinical trials. Today, many CROs have expanded their scope of services to provide comprehensive management of the entire drug development process for their client companies. The CRO market grew from $1 billion in 1992 to more than $8 billion in 2002.

The transition to contract research has been justified by the pharmaceutical industry as necessary to bring their products through the testing and regulatory process in a rapid, cost-effective manner. Until the 1980s, academic medical centers were the primary source for clinical trial research into potential new drugs; and the researchers were largely independent of the companies that sponsored their work. In 1990, about

80 percent of industry–sponsored trials were done at academic institutions. Within a decade that dropped to 40 percent. Marcie Angell observed, "As they became richer, more powerful, and more profit–driven, drug companies became less willing to sit back and wait for academic researchers to produce their results." Extended time in clinical trials meant the drug companies have less time to exclusively sell the drug once it is approved by the FDA. For a "blockbuster" drug every additional sales year before it is sold as a generic can mean additional billions in revenue for the parent drug company. Now drug companies are involved in every detail of the clinical trial research for a new drug: "from design of the study through analysis of the data to the decision to publish the results." Company sponsors, not the researchers now control the clinical trails; and the potential for bias had increased immensely.

For instance, a survey of seventy articles on the safety of channel blockers (used to treat high blood pressure, angina and some abnormal heart rhythms) found that 96 percent of the authors who were supportive of the drugs had financial ties to the companies that made them. "Only 37 percent of the authors critical [of the drugs] had such ties." A recent survey found that industry–sponsored research was almost four times as likely to be favorable to the company's product as NIH–sponsored research.

A 2001 *Washington Post* article entitled "Missing Data on Celebrex" related how a study published in *The Journal of the American Medical Association* showed that Celebrex had fewer side effects than two older arthritis drugs. A favorable editorial for using Celebrex accompanied the published article. After the article was published, the editors of JAMA discovered that the study results were based solely on the first six months of the yearlong study. "When the entire trial was analyzed, there was no advantage to Celebrex." The study was sponsored by the makers of Celebrex.

Dr. Angell comments: "There is a general inflation in the notion of the good that drugs can do (and a corresponding deflation in concern about side effects)." We see this inflated notion with a closer examination of antidepressants, generally accepted as highly effective drugs.

Effectiveness of Antidepressants

In 1998 Irving Kirsch and Guy Sapirstein did a meta–analysis of research studies into the effectiveness antidepressant medication and found that 75% of the response to antidepressants was duplicated by placebo; only 25% of the drug response could be attributed to the medication. There was a .90 correlation between the placebo effect and the drug effect. They concluded "that virtually all of the variation in drug effect size was due to the placebo characteristics of the studies." The findings were surprising, even to the researchers themselves, because of the widely held belief in the effectiveness of antidepressant medication.

Their original intent was to study the placebo effect; and while they expected to find a substantial placebo effect, they did not expect such a small medication effect. Not surprisingly, the study provoked a significant discussion on its findings. So Kirsch was receptive to the suggestion that he replicate his study, using the clinical trial data submitted to the FDA by the pharmaceutical companies. When seeking approval for their medications, drug companies are required to submit all of their clinical trial data. Many, if not most, of the objections with his original study would not apply to the data submitted to the FDA for approval of antidepressant medications.

Kirsch and his fellow researchers analyzed the data submitted to the FDA for the six most widely prescribed antidepressants between 1989 and 1999: Prozac (fluxetine), Paxil (paroxetine), Zoloft (sertraline), Effexor (venlafaxine), Serzone (nefazodone), and Celexa (citlaopram). The study found that only 18% of the drug response was due to the pharmacological effects of the medication; 82% of the response to antidepressants was duplicated by placebo. The data used by the FDA to support the approval of the above noted antidepressants had a greater placebo effect than the studies analyzed by Kirsch and Sapristein in their 1998 study!

Kirsch and the authors of the 2002 study suggested that the even greater differences may be due to two factors: publication bias and missing data within the studies assessed in 1998. In the 2002 study by Kirsch et al., publication bias was controlled for by using all the data submitted to FDA for approval of the above noted antidepressants; and a statistical calculation that circumvented the missing data problem. There was a small (less than two points) but statistically significant drug effect noted in the 2002 study, when improvement was measured by the Hamilton Depression Scale. However, the significance of this small difference is of questionable clinical value.

Walter A. Brown, of Brown University, responded to the Kirsch et al. (2002) study by acknowledging that antidepressants are not as good as the hype by the pharmaceutical industry would have us believe. He then suggested that antidepressants may have more inherent effectiveness than they appear to have in clinical trials. First, the clinical trials process enhances the likelihood of a placebo response. People report greater improvement simply because they expect to improve as a result of being in a clinical trial for a new medication. There are elements to the placebo effect that mobilize hope and relieve stress with a depressed patient: contact with an expert healer; a thorough evaluation; an explanation (diagnosis) for the distress; an expectation of improvement; commitment, enthusiasm and positive regard from the clinician; the opportunity to verbalize stress; and a plausible treatment.

Brown also suggested that antidepressants look as ineffective as they do because they are given to the wrong patients. The inclusion and exclusion criteria for clinical trials and the demands of participating in the clinical trial process rules out the more severely depressed patients. So participants in the clinical trials "tend to fall toward the mild end of the depression spectrum." This population bias within clinical trial research is important because patients with milder depression have been found to be more responsive to the placebo effect, while the most severely depressed patients, those who require hospitalization, seem to respond better to medication. Brown then concluded:

"Kirsch et al.'s (2002) article reminds us that antidepressants are not as good as their hype would have us believe. It also reminds us that simply being treated—even with placebo—can be a powerful antidote for some types of depression. But the meager effects of antidepressants . . . may result more from their use in unsuitable patients than from essential ineffectiveness. One size doesn't fit all."

In summary, antidepressants are not as good as their hype would have us believe. Within the same clinical trials used to gain approval for their sale through the FDA, the effectiveness of antidepressants was just marginally greater than a concurrent placebo effect. Participants in these clinical trails tended to be from the milder end of the depression spectrum and seemed to respond more readily to the placebo effect. Patients with more severe depression tended to be excluded from clinical trials and seemed to respond better to medication.

The significance of this analysis is that the **very same data** used by the drug companies to gain approval from the FDA to bring to market six current antidepressant medications suggests that their effectiveness, in many cases, can be duplicated by a "placebo effect." The marginally greater influence of medications, as measured by the Hamilton Depression Scale, has no real clinical impact. The mean difference between medication and placebo is less than the scoring range (0 to 3) for one item on the Hamilton Depression Scale.

The use of antidepressants as the initial intervention into milder forms of depression may not be the best course of action, especially with the growing evidence for negative (and even) harmful side effects with them. Concerns ranging from addiction (discontinuation syndrome) to suicidality, violence and temporary psychosis have been reported to occur with antidepressants. See breggin.com for more information, especially "Suicidality, Violence and Mania Caused by Selective Serotonin Reuptake Inhibitors (SSRIs): A Review and Analysis;" originally published in the journals *International Journal of Risk and Safety in Medicine* and *Ethical Human Sciences and Services.*

There is a growing body of evidence that cognitive therapy may be as effective as medication with moderately to severely depressed patients; both during the initial phase of treatment and in preventing a recurrence of the treated episode of depression (relapse). Robert DeRubeis of the University of Pennsylvania found that during 16 weeks of initial treatment, 58% of moderately to severely depressed patients had a favorable response to cognitive therapy; the same as for patients on antidepressants. When the two groups were compared one year after withdrawing from treatment, cognitive therapy had an enduring effect that seemed to make it at least as effective in preventing relapse as keeping patients on medication. These findings challenged American Psychiatric Association (APA) guidelines, which state the most people with moderate to severe depression should take antidepressants. Since the publication of DeRubeis' study, the APA has said it will be taken into consideration when the guidelines are updated. See the DeRubeis lab at psych.upenn.edu/~derubeis for pdf files of the above cited articles originally published in 2005 in the *Archives of General Psychiatry*.

Also see the following for further discussion of the findings on the effectiveness of antidepressants:

Kirsch and Sapirstein (1998). "Listening to Prozac but hearing placebo: A meta-analysis of antidepressant medication." *Prevention and Treatment,* volume 1.

Kirsch et al. (2002). “The Emperor’s New Drugs: An analysis of antidepressant medication data submitted to the U.S. Food and Drug Administration.” *Prevention and Treatment,* volume 5.

Brown, Walter A. (2002) “Are Antidepressants as Ineffective as They Look?” *Prevention and Treatment,* volume 5.