Considerations of net present value in policy making regarding diagnostic and therapeutic technologies

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Background The pharmaceutical and medical device industries function in a business environment in which shareholders expect companies to optimize profit within legal and ethical standards. A fundamental tool used to optimize decision making is the net present value calculation, which estimates the current value of cash flows relating to an investment.

Methods We examined 3 prototypical research investment decisions that have been the source of public scrutiny to illustrate how policy decisions can be better understood when their impact on societally desirable investments by industry are viewed from the standpoint of their impact on net present value.

Results In the case of direct, comparative clinical trials, a simple net present value calculation provides insight into why companies eschew such investments. In the case of pediatric clinical trials, the Pediatric Extension Rule changed the net present value calculation from unattractive to potentially very attractive by allowing patent extensions; thus, the dramatic increase in pediatric clinical trials can be explained by the financial return on investment. In the case of products for small markets, the fixed costs of development make this option financially unattractive.

Conclusions Policy decisions can be better understood when their impact on societally desirable investments by the pharmaceutical and medical device industries are viewed from the standpoint of their impact on net present value. (Am Heart J 2008;156:879-85.)

Public attitudes toward the drug and device industries are increasingly negative. Opinion surveys in the United States rate pharmaceutical companies on par with tobacco companies in terms of how they consider the welfare of their customers.[1] Likewise, accusations regarding the withholding of important safety information about product defects have cast a shadow over the medical device industry.[2] Nevertheless, the public remains supportive of bringing new drugs and devices to market.

It is possible that these problems result from poor decisions about individual products that are dangerous or harmful to the public. Although this may be true in some cases, an alternative view is that firms can act within the bounds of accepted, legally appropriate behavior and still make decisions that are adverse to public health. Moreover, when this happens, such behavior is a response to the question, "What action that is within legal and ethical norms will lead to the maximum profit for our shareholders and our company?" A tool that is commonly used to make such decisions is the "net present value" calculation, which couches decisions in terms of the total future impact on the finances of the entity making the decisions. In the narrowest sense, this is a simple financial calculation. At a broader level, firms can consider other intangible contributions to this financial assessment, including public perceptions of the firm or the potential threat of regulatory action.[3]

Our premise is that public policies related to the pharmaceutical and device industries foster an environment in which individual decisions about products and aggregate decisions about product portfolios within companies create opportunities to maximize net present value while pursuing scenarios that are adverse to public health. A broader understanding of net present value calculations by clinicians, the public, and policy makers could have positive effects on drug and device development for at least 2 reasons. First, an understanding of firms' perspectives in assessing net present value would enable providers to better comprehend the decisions that are being made by them. Second, an overt effort to consider the impact of public policies on net present value might enable policy makers to better reconcile the incentives on companies with the public good.

Net present value

The present value of an expected future cash flow is today's value of that cash flow. To calculate present value,

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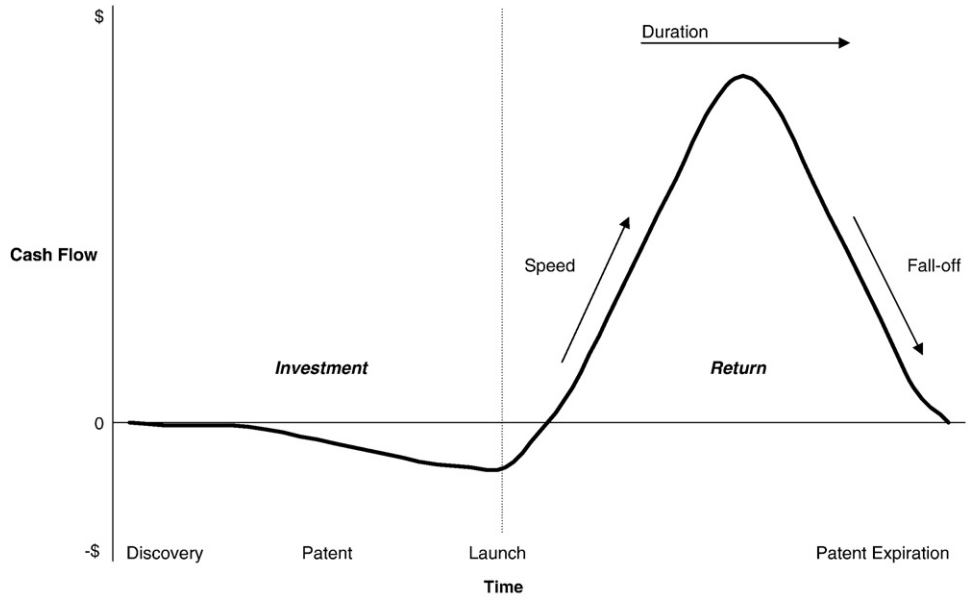
Figure 1



Cash flows from an investment in a new medical product. The return on the investment is dependent on the speed, duration, and falloff of the area under the return curve. Policy changes can affect any of these 3 parameters and the return on investment for the firm.

we need to know how far in the future the cash flow will be received and how confident we can be about its timing and size. The farther away and the "riskier" (more uncertain) the future cash flow, the less the cash flow is worth today. The application of a discount rate to future cash flows is critical to this analysis. The discount rate represents the preference for a dollar today compared with a dollar at some time in the future. The discount rate also includes adjustment for the amount of uncertainty about future cash flows. Thus, present value at time t can be calculated as follows, where PV is present value, NCF is net cash flow (receipts minus payments) at time t, and r is the discount rate:

$$\mathrm{PV} = \frac{\mathrm{NCF}}{(1+\mathrm{r})^{\mathrm{t}}}$$

The net present value of a project is the sum of the present values of all such net cash flows related to the project, both negative (ie, payments) and positive (ie, receipts). In risky endeavors such as drug development, in which firms accrue costs for several years before receiving revenues, future revenues are discounted heavily in the calculation of net present value. Figure 1 shows these positive and negative cash flows from the perspective of a firm. Policies that increase research costs or increase the time from discovery to market increase the size of the investment required. Policies that negatively impact the rate of adoption of a product that has been approved for marketing (or push back the timing of reimbursement decisions) will tend to decrease returns on the investment.

Table I shows the net present value calculation for 2 very simple scenarios in which costs total $100 million and are incurred today. In one scenario, the project is expected to generate $250 million in revenue; in the other, the project is expected to generate $120 million. One might conclude that the project is worthwhile because the costs are covered even in the worst-case scenario. However, when we consider that the revenues will be earned in the distant future, while costs are incurred right away, the conclusion is less clear. If we assume that revenues are expected 5 years from now and that the appropriate discount rate is 11%, the project will result in a significant financial loss in the second scenario. The higher the discount rate, or cost of capital, the lower the value today of future returns from long-term investments.

Discount rates for these analyses have been met with skepticism in the health care literature.[4-9] The discount rate for public firms is calculated based on the cost of capital used by those firms, which includes the proportion of debt and equity capital issued by the firm and the risk of the firm relative to the overall performance of financial markets.[10] The cost of capital is the financial return required by the firm to pay the

Table I. Calculation of net present value for 2 simplified scenarios

Variable	Scenario 1	Scenario 2
Probability (%)	50	50
Revenues, millions ($)	250	120
Present value, revenues, millions ($)	$250/(1.11)^5 = 148$	$120/(1.11)^5 = 71$
Present value, costs, millions ($)	−100	−100
Net present value, millions ($)	−100 + 148 = 48	−100 + 71 = −29

Table II. Potential outcomes of a decision about whether to conduct a head-to-head comparative clinical trial

Variable	No clinical trial	Product is superior	Product is inferior
Present value, revenues, millions ($)	$150/(1.11)^2$= 122	$270/(1.11)^2$ = 219	$30/(1.11)^2$ = 24
Present value, costs, millions ($)	0	−25	−25
Net present value, millions ($)	122	−25 + 219 = 194	−25 + 24 = −1

suppliers of its capital, including bondholders and equity shareholders. In other words, if the firm cannot make this required rate of return, shareholders and bondholders would prefer that the firm return the investment dollars because the investors presumably could improve the risk-return trade-off through other investments. For this reason, the discount rate represents the "opportunity cost" of investments for the firm, in that it is the minimum return required from investments in new projects to achieve these return benchmarks. Most firms face a cost of capital of ≥10%, although these costs "float" with market conditions. By comparison, government investments are considered risk-free and thus have a much lower cost of capital (currently 4% to 5% for risk-free instruments). It is clear that calculations of net present value for large future cash flows are sensitive to the choice of the discount rate.

Calculating net present value using probability-weighted revenues

An alternative method of calculating the net present value of a project is to estimate the expected revenue by probability-weighting the revenue scenarios. If we assume that the 2 scenarios are equally likely to occur, then the expected revenue is calculated as $250 million × 50% + $120 million × 50% = $185 million. The present value of the expected revenue can then be calculated as $185 million/$1.11^5$ = $110 million. Finally, the expected net present value of the project is $110 million − $100 million = $10 million.

One problem with the model of expected net present value is that it offers no insight into the extremes of the possible outcomes. Although the expected net present value is positive (at $10 million), half of the time this project will result in a significant loss. If the second of the 2 scenarios is more likely than the first scenario (≥63% chance), the whole project has a negative expected net present value.

Methods

We considered 3 investment decisions that pharmaceutical and device companies commonly face. In the first scenario, a company has a product that lowers mortality in a chronic disease compared with placebo, and thus the product is on the market. Another product on the market has also been shown to lower mortality in the same disease compared with placebo. The company must decide whether to conduct a comparative clinical trial that would clarify which product is superior. In the second scenario, a company must decide whether to conduct a pediatric extension trial as its drug enters the market. In the third scenario, a company must decide whether to develop a product if it will be entering a niche market with modest potential for profit. These scenarios are modeled using decision analysis techniques, which allow for assessments of alternative scenarios under conditions of uncertainty.[11]

Should a company fund a clinical trial that might show its product to be inferior to a comparator product?

The public, health care providers, and policy makers frequently express frustration about the scarcity of evidence from direct comparative clinical trials that would enable better choices about therapies.[12] Yet, the potential financial implications of choosing to undertake such a trial explain why so few of the trials are conducted by companies acting on their own. If there is no head-to-head trial, we might assume that the total market for the drug is $300 million and that the 2 companies will each capture approximately 50% of the market, or $150 million. If we also assume that this revenue will be received 2 years in the future, the present value of the revenue stream is $122 million (assuming an 11% discount rate).

Alternatively, a clinical trial comparing the 2 products will cost $25 million, and we might assume that the superior product will capture 90% of the market ($270 million). Table II shows the potential outcomes of a decision about whether to conduct the clinical trial. The calculations show that, if the company's product is inferior, a comparative trial would likely threaten expectations for the product and potentially the firm's future profitability. In the analysis, if the potential for a positive result in the head-to-head trial is <63%, the firm is better off not conducting the trial (Table III). Moreover, even if the product is truly superior, the clinical trial would be subject to type II error, which could result in the absence of a superiority finding. This type of error could arise from problems in study design, underestimates of the required sample size, or statistical chance. Thus, the firm might consider the range of potential outcomes from the study, not

Table III. Effect of type II error on net present value in a decision about whether to conduct a head-to-head comparative clinical trial

Net present value with no clinical trial, millions ($)	Probability of superiority in a clinical trial	Net present value with clinical trial, millions ($)			
		No type II error		Type II error (β = .2)	
		Trial	Trial vs no trial	Trial	Trial vs no trial
122	1.00	194	72	155	33
122	0.90	175	53	140	18
122	0.80	155	33	124	2
122	0.79	153	31	122	0
122	0.78	151	29	121	–1
122	0.77	149	27	119	–3
122	0.76	147	25	118	–4
122	0.75	145	23	116	–6
122	0.74	143	21	115	–7
122	0.73	142	20	113	–9
122	0.72	140	18	112	–10
122	0.71	138	16	110	–12
122	0.70	136	14	108	–14
122	0.69	134	12	107	–15
122	0.68	132	10	105	–17
122	0.67	130	8	104	–18
122	0.66	128	6	102	–20
122	0.65	126	4	101	–21
122	0.64	124	2	99	–23
122	0.63	122	0	98	–24
122	0.62	120	–2	96	–26
122	0.61	118	–4	94	–28
122	0.60	116	–6	93	–29
122	0.50	97	–25	77	–45
122	0.40	77	–45	62	–60
122	0.30	58	–64	46	–76
122	0.20	38	–84	31	–91
122	0.10	19	–103	15	–107
122	0.00	–1	–123	–1	–123

just the best outcome, in considering an investment in comparative studies (Table III). In this scenario, assuming statistical power of 80%, the probability of demonstrating superiority would have to exceed 79% for the investment in a clinical trial to be financially attractive.

Should a company conduct a pediatric extension trial to evaluate a drug that already has a role in adults?

When contemplating whether to conduct a pediatric trial of a drug that is used commonly in adults, a company must consider both the cost of the trial and the small incremental market for the drug, even if it is found to be beneficial. As an incentive to conduct such trials, the US government has extended the patent life of products for which pediatric clinical trials have been undertaken (http://www.fda.gov/cder/pediatric/).

Table IV shows the net present value calculation for this scenario. Before the policy change regarding patent life, conducting a pediatric trial would have resulted in a financial loss. After the policy change, the company realizes a financial gain, but this result is driven by the patent extension and additional sales for adult patients rather than by the incremental market for pediatric patients.

Table IV. Calculation of net present value for a decision about whether to conduct a pediatric extension trial

Cost of pediatric trial	–$25 million
Duration of pediatric trial	1 y
Annual profits under patent	$150 million
Potential pediatric sales if trial is positive	$10 million 1 y from now
Present value assuming an 80% trial success rate	$7 million
Net present value of pediatric trial, net of pediatric trial	–$18 million
Patent extension	6 m
Incremental profit from patent extension	$75 million 1 y from now
Present value of incremental profit	$68 million
Net present value of pediatric trial, net of pediatric trial cost without considering pediatric sales	$43 million
Net present value of pediatric trial, net of pediatric trial including pediatric sales	$50 million

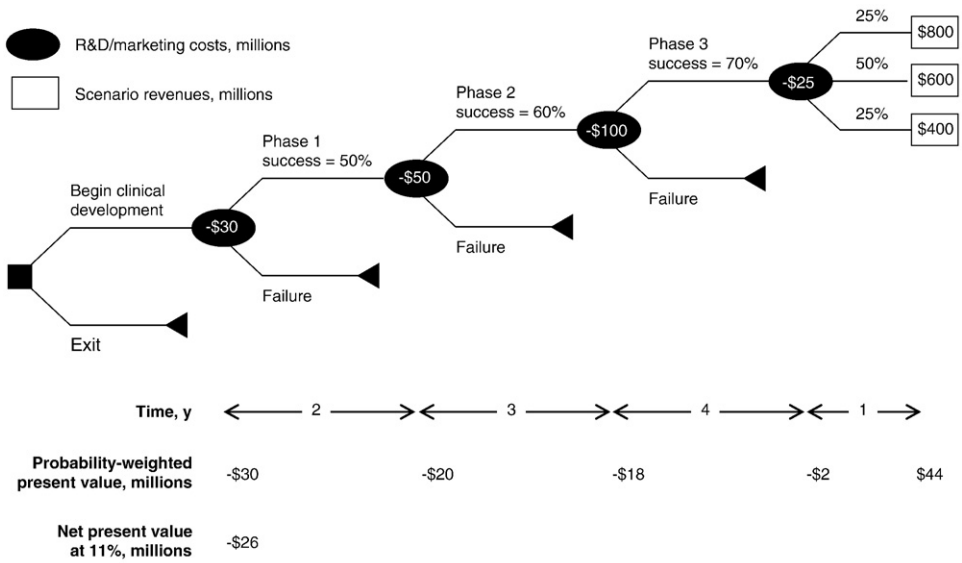
Should a drug be developed if it will have only a small market?

The drug development process is characterized in part by the need for significant investments in product development years before a product comes to the market. It is also characterized by a high failure rate of individual products. Given the current regulatory structure for drug approval, the costs of drug development are relatively fixed, regardless of the size of the market for the product being developed (with exceptions in certain cases for HIV therapies, cancer therapies, and orphan drugs). For example, the costs of toxicology testing, long-term animal studies, human safety studies, and human pharmacokinetic and pharmacodynamic testing would not differ for a drug aimed at a small market as compared to a large market. Moreover, large-scale efficacy studies might be even more expensive in a smaller market because of the need for a larger number of trial sites and the potential for slower recruitment of patients. If a company has a compound with significant potential for benefit, but in a limited market, how would the company respond to the investment opportunity?

Figure 2 shows the general net present value calculation for drug development. In this scenario, if a company has a product with an estimated market size of $400 million to $800 million, it would have a negative expected return on investment in the current environment. Thus, the firm would decide not to pursue the investment. Alternatively, given a limited market size, the firm could consider increasing the price of the product to the point where the net present value was positive. In this case, the price of the product would have to increase by >60% for the investment to have a positive net present value.

Given the limited management time and financial resources of a single firm, companies must restrict their efforts to a limited set of projects. Projects with the lowest potential

Figure 2



Net present value calculation for drug development. Each cost is multiplied by the cumulative probability that it will be incurred and discounted at 11% over the appropriate number of years. For example, the probability-weighted present value of phase 3 costs, in millions, are as follows: ($100) × (0.50) × (0.60)/(1 + 0.11)^5 = $18.

financial returns are less likely to be undertaken by a firm unless there are no suitable alternatives for investment.

Discussion

The hypothetical scenarios underscore the disconnect between what is desirable from a societal perspective and what companies do to maintain their profitability in a competitive market. Although net present value can vary substantially depending on the details of the individual case, these scenarios illustrate decisions faced almost every day in the pharmaceutical and device industries.

The first scenario suggests not only that companies have little incentive to conduct head-to-head clinical trials but also that conducting such trials can be adverse to their financial security. The perception of those who make decisions about the use of products is a critical intangible in any net present value calculation because it is not the actual benefit of a product that matters but the perceived benefit from the perspective of those making the investment decision. This results in a dilemma for the public and for policy makers. The public benefit that could result from improved data about clinical products will not be produced spontaneously by industry under the current set of incentives and governance structures. In the absence of changes in the regulatory environment, alternative sources of support may be required to fund these studies. Indeed, this has been done multiple times, as in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial sponsored by the National Institutes of Health (Bethesda, MD). However, the amount of federal funding available for such trials has been small, and other funding sources such as health systems and insurance companies have failed to see such trials as useful investments. The new enthusiasm for comparative effectiveness studies at the federal level may reverse this historical pattern.[12] Finally, it may be that a combination of federal funding and financial incentives for companies willing to cosponsor such trials would be the most successful approach.[13,14]

The second scenario, in which a company must decide whether to conduct a pediatric extension trial, is a "slam dunk" for public policy making. Before the US government began granting patent extensions based on these studies, few trials were conducted in children, despite the widespread use of drugs in children. Ethical concerns were often cited as the basis for failing to conduct the necessary trials, as concerns were raised about the feasibility of conducting experiments on children. However, the pediatric community realized that, in the absence of controlled trials, every child was effectively an experimental subject receiving therapies without adequate information about dosing and safety; this led to the term *therapeutic orphans* to describe children.[15] Because of persistent lobbying, the Pediatric Extension Rule was enacted, granting 6-month patent extensions based on conducting an informative trial, regardless of whether the result was positive or negative. Suddenly, the

impossible trials in children became possible, and >150 patent extensions have now been granted, with a resulting increase in information about the use of drugs in children.[16-21] However, the efficiency of this approach can vary markedly across products.[22]

The final scenario is an explicit depiction of a major societal problem. Potentially useful drugs are routinely dropped from drug development portfolios, and new uses of approved drugs frequently are not pursued, because of the potential financial risk of negative trials and the sheer cost of drug development. From the perspective of the company, financial incentives clearly dictate one choice over another. Policy approaches to the issue of development choices are complex and difficult. One approach would be to provide incentives for companies to develop effective treatments for diseases that have been targeted as being in particular need for better therapies. This is being undertaken by the World Health Organization and the US government with regard to HIV treatment and vaccination. A second approach would be to provide funding directly from private sources, such as philanthropic or charitable organizations. The Food and Drug Administration (Rockville, MD) has an "orphan disease" designation that allows for special support of research efforts for diseases identified as having a small potential market but a great need.[23,24] Investment may be particularly sensitive to efforts to reduce the costs of clinical trials, reduce the duration of the premarket stages of clinical development, subsidize the costs of investment, or support higher prices for products in smaller markets. For the wide array of diseases, however, some combination of the above approaches coupled with efforts to generally reduce the cost of clinical trials will be needed.[25]

The scenarios also highlight an issue that cannot be ignored in the debate about the behavior of pharmaceutical and device companies. For products that do not directly affect human health, markets provide an efficient means for consumers to choose among alternative ways to spend their money. The market for drugs and devices is less fluid than other markets because of restrictions on entry resulting from the years of testing and development required to achieve regulatory approval. Also, the products may not have direct substitutes, another attribute of more fluid markets. Finally, even when firms' financial returns are related to the prices of their products, ethical problems arise related to access to these products for individual patients, or fiduciary issues are raised for third-party payers over distribution of pooled resources from groups of beneficiaries. This need for significant investment with high risk and limited ability to raise prices within niche markets leads to complex choices about product development and should be considered in policy decisions. For example, it has been clearly established that neither physicians nor patients can determine the net balance of benefit and risk of a drug from individual experience. Although firms are reluctant to invest in studies to inform this choice, there are undoubtedly situations in which patients would benefit from pragmatic clinical trials to provide unbiased estimates of the beneficial and detrimental effects of chronic treatments, rather the relying solely on individual physicians' clinical experience.[26,27]

These analyses characterize the dissociation between decisions that will maintain the required returns for companies and the decisions they could make to improve public health. Providers and regulators who consider these parameters will be better informed about how they might influence private investment decisions in a positive manner. By considering policy decisions through this framework, we could reduce the dissociation between financial viability of firms and the public health.

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