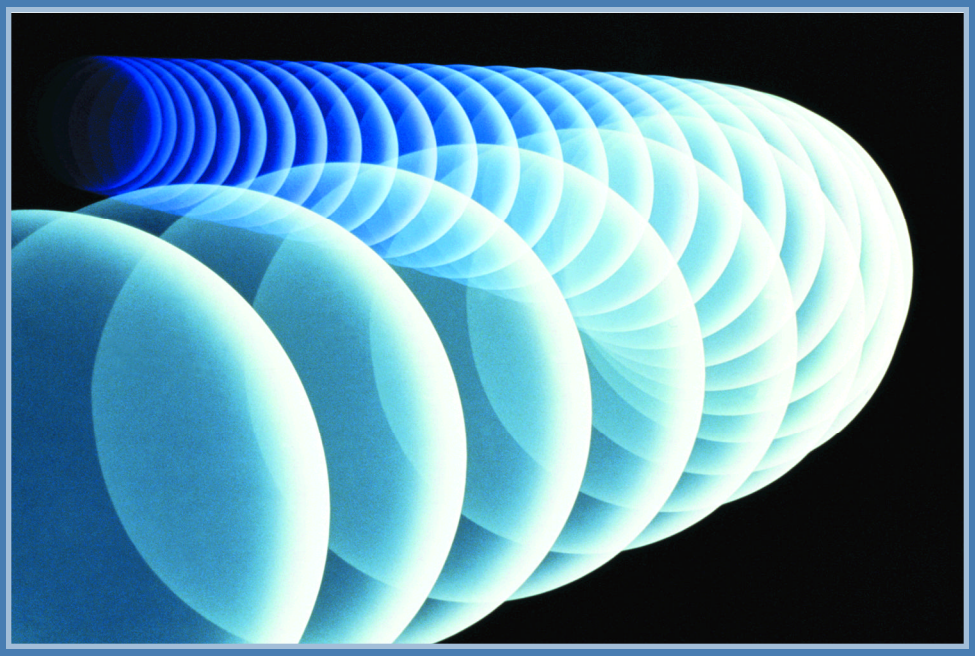


Over the past decade, option theory has received a great deal of attention from both academia and business. Avinash K. Dixit (Professor of Economics at Princeton University) and Robert S. Pindyck (Mitsubishi Bank Professor of Applied Economics in the School of Management at the Massachusetts Institute of Technology) have asserted that "in order to make intelligent investment choices, managers need to consider the value of options." Judy Lewent, CFO at Merck & Company, has suggested that "all business opportunities are real options." A number of strong performers in the pharmaceutical industry – including Merck – now view their investment opportunities as real options. They manage their options proactively to create value and take advantage of the inherent flexibility of options when resolving uncertainties. But other companies still live in a static world of planning based on discounted cash flow. These companies do not recognize that the rigid execution of a plan can destroy value when funding is committed in full up front.

Capturing Value from Optionality in Pharma R&D

Birgit König, Aleksandar Ruzicic, Michael Schuppenhauer, Thomas Sepp

We believe that the R&D process at any pharmaceutical company can benefit from the guidelines that option theory supplies. Basically, any staged investment that gives managers the right to invest further but does not require them to do so is an option. The flexibility inherent in these options can be highly valuable, and the value can be increased if the investments are managed according to option theory.

Nonetheless, executives at many pharmaceutical companies have not yet recognized or applied the power of real options in their businesses – despite the apparent relevance of option theory to pharmaceutical R&D. Some assert that the theory is too mysterious, that its "black box" characteristics make it difficult to gain organizational buy-in. Some tools for option valuation seem too simplistic, while others seem overly complex. We would argue that option valuation could be as transparent as decision tree analysis and as easy to implement. Additionally, executives can reap the benefits of managing according to option theory without becoming deeply conversant with real option valuation techniques. We believe that managers who experiment with real option valuation will discover that:

- Real option valuation is the best valuation tool for most life sciences development projects
- Early projects can be effectively evaluated using options
- The value of options increases with uncertainty, flexibility, and learning efficiency, when uncertainties are resolved over time and management has the flexibility to react accordingly.

The Best Valuation Tool for Most Pharma Projects

Many managers in the pharmaceutical industry doubt that financial valuation of an R&D project adds any value in early decision making. It seems that the same reasons against a quick real option valuation (ROV) adoption are cited today, as historically for the net present value (NPV) method. Real option pricing, however, can be an effective way to assess alternative deal structures and to introduce ever more valuable degrees of flexibility – even if the results seldom match intuition. With licensing, for example, the importance of accurate financial evaluation becomes obvious. If a company offers too low a price in the bidding process, it risks losing valuable compounds. If it overpays, it destroys value. The problem is made even worse with flexible licensing deal structures, which feature milestone and royalty payments and equity transfers in addition to up-front payments.

Managerial corporate finance theory has been struggling for years with the question of how to evaluate investments in conditions of uncertainty, and many different methods have been applied. Much of the criticism leveled at the financial valuation of pharmaceutical R&D projects is due to the fact that discounted cash flow (DCF) is the most popular approach, an approach that cannot even remotely capture the option value in R&D projects. DCF assumes that companies hold investments passively. It ignores management's flexibility to alter the course of a project in response to changing conditions; thus it creates a static picture of existing investments and opportunities. Practitioners who are aware of DCF's shortcomings tend to rely on techniques such as scenario analysis or simple decision tree analysis (DTA). Both methods, as commonly implemented, recognize that uncertainty exists, but do not value flexibility or adjust for risk. Only real option valuation encompasses both flexibility and the resolution of uncertainty through learning, and, therefore, the "true option value" of a pharmaceutical project. Why is this?

In the financial assessment of Pharma R&D development projects, the choice of method depends on level and type of uncertainty (Exhibit 1).

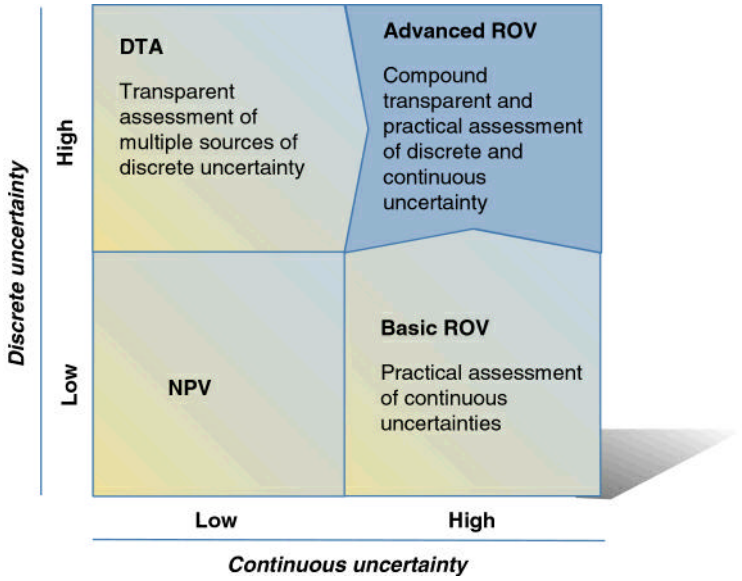
DCF can only be used when there is no flexibility to react to outcomes – not a typical situation in Pharma R&D. In such a case, any uncertainty of input parameters for a classical NPV calculation with DCF can be captured through Monte Carlo scenario analysis. The Monte Carlo methodology returns the uncertainty of the NPV, based on the uncertainty assumptions for the input parameters.

DTA is a rigorous decision tool, widely used in the pharmaceutical industry and rightly the method of choice when (discrete) technical uncertainty predominates. However, DTA cannot capture any continuous market uncertainties like the level of off-label prescriptions or disposable income in the case of lifestyle drugs. It will, therefore, underestimate the value of most ethical and all over-the-counter drugs.

Basic ROV according to the original Black-Scholes formula can capture project value correctly whenever the

Exhibit 1

CHOICE OF QUANTITATIVE EVALUATION METHOD



uncertainties affecting project value are mainly of continuous nature. Where this is the case, as in natural resource valuations, basic ROV has already started to replace DCF in practice. The key to the easy application of the method is a reliable volatility estimate for the natural resource price, such as oil, which can be derived directly from the financial markets. The Chicago Board of Trade started trading in futures on crude and heating oil in 1983. Today, oil companies have to evaluate whether financial options or real options (i.e., capacity shutdown), is the method of choice to maximize revenues to shareholders (Martha Amram and Nalin Kulatilaka: Real Options: Managing Strategic Investment in an Uncertain World). However, in most pharmaceutical applications, basic ROV is of little help, as it cannot properly capture discrete uncertainties such as technical success or entry by a competitor. It thus overvalues projects significantly.

Advanced ROV can handle a high level of both discrete and continuous uncertainties. It is thus the only method that correctly captures the economic features of a typical R&D project. It is always correct, and when uncertainties from many different sources have to be modeled, it is much more practical than other methods, because there are opportunities for simplification. Apparently only the continued misperception that this theory is complex prevents more people from applying it and from initially preferring NPV methodology.

In fact, if you can implement DTA, it is not much work to implement advanced ROV. The evaluation of a pharmaceutical project with advanced ROV generally follows a five-step approach (Exhibit 2):

1. Calculate base case: As a basis for the valuation, the target profile of a drug is described. An ordinary DCF calculation based on this target profile will be used later to evaluate the relative importance of different uncertainties.
2. Identify uncertainties and flexibility: Uncertainties about input variables are identified and characterized for level and type. For discrete uncertainties, probabilities of events are specified; for continuous uncertainties, ranges of outcomes should be specified.
3. Build an event tree: The most important uncertainties (i.e., those with the greatest effect on value) should be modeled explicitly. This will prevent valuation models from becoming overly complex. On the basis of the major discrete uncertainties, an event tree should be developed. It will incorporate discrete uncertainties as individual branches with time of resolution and probabilities. The continuous evolution of the project market value is modeled as up-and-down movements in the event tree.
4. Simulate magnitude of volatility: The remaining discrete and continuous uncertainties should be combined into the "volatility of the project market value," as derived from Monte Carlo simulation. Additionally, because the learning about this bundled uncertainty can be assumed to be constant, the resultant volatility used for calculations in the Black-Scholes formula will be constant as well.
5. Determine project value: For each state of nature or "end point in the tree," the market value is determined.

Exhibit 2

PROCESS FOR CALCULATING PROJECT VALUE

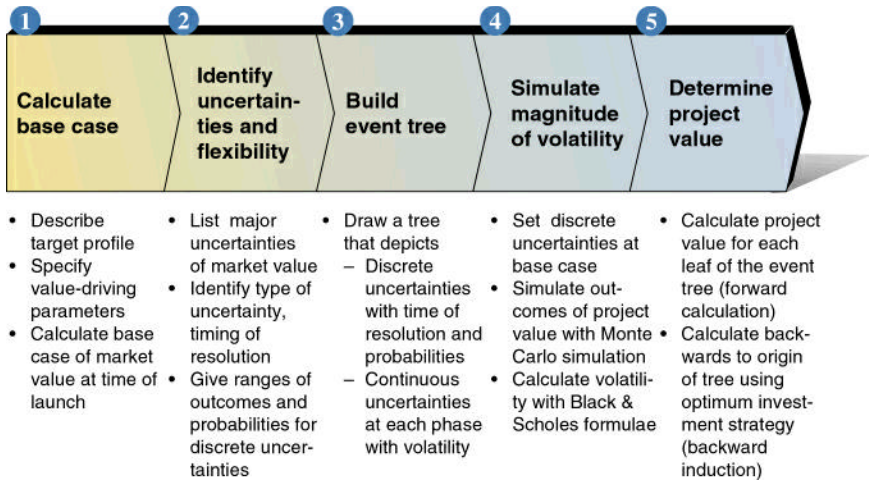
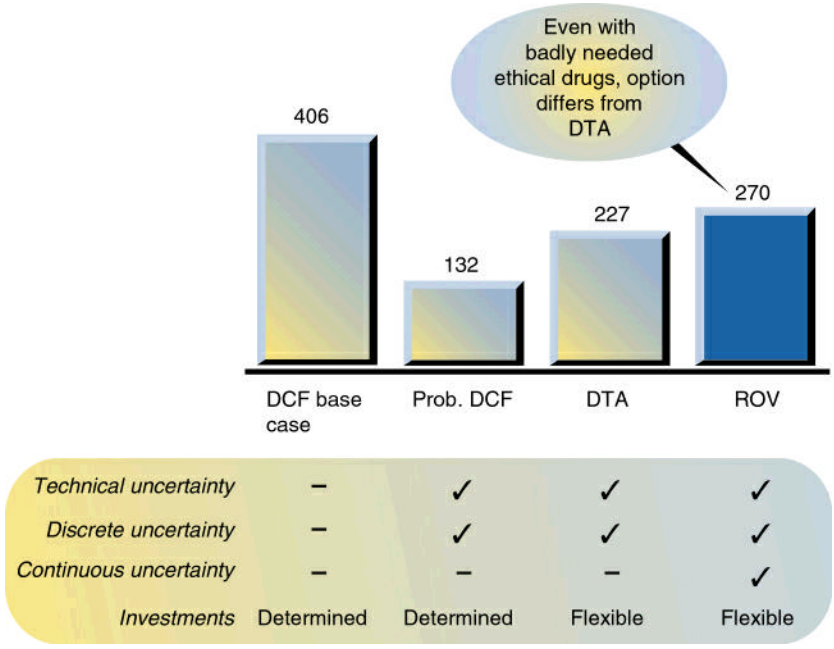


Exhibit 3

COMPARISON OF PROJECT VALUE BY METHOD*

$ Millions



* Project value including investments at t = 0

Source: McKinsey analysis

Backward induction of this tree then yields the true project value, assuming a "rational" investment decision at each decision point. An investment decision is considered rational only if the expected value at a certain decision point is higher than the investment needed to complete the next phase of development.

As these steps make clear, advanced ROV is really a decision tree overlaid with a real option lattice. It unites the advantages of both methods: It makes decisions along the development path transparent and is thus easily understood by R&D personnel. It also supplies a convenient method to deal with the multitude of minor risks and market uncertainties through bundling into one uncertainty, and it gives correct results, even for OTC and generic drugs (Exhibit 3).

Worthwhile for Early Projects

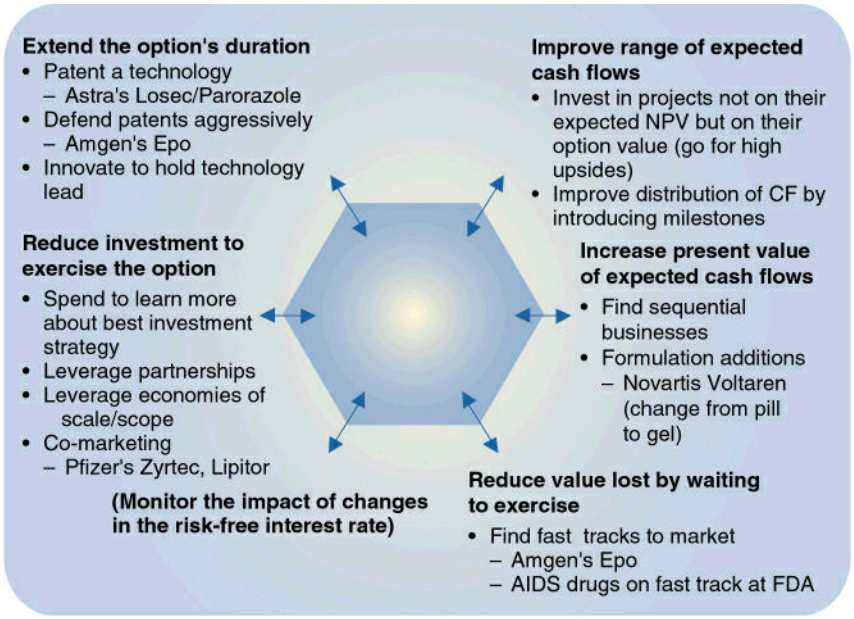
Option valuation is the method of choice for most development projects, but what about those early projects that do not justify an elaborate financial evaluation? Usually, companies do not require a dollar amount of project value, but an internal ranking. In these situations, many companies use a rough DCF calculation of a "base case," together with a risk assessment to determine a project's rank. Evaluated from a DCF point of view, a project with high risk is less attractive than a project with low risk.

Here again, because it discriminates against risk and does not recognize the value of flexibility, DCF is misleading. To acknowledge option value in investment decisions of very early projects, two main evaluation parameters should be "upside market potential" and

"timing of resolution of major uncertainties." Successful companies actually display an appetite for risk when selecting R&D projects. They understand that "risk" means an increase in the volatility of a project's value and, therefore, that risk has both a downside and an upside. If management can avoid some of the less attractive outcomes by being flexible in its decision making – for example, by walking away from the original investment decision, changing the nature of trials, reorienting the targeted claims – the project's value distribution becomes skewed and the mean value increases. Assuming about the same flexibility for all projects in this stage, project value is thus determined mainly by the upside, not by the downside. Of course, the earlier uncertainty is resolved the more valuable the project becomes. Thus, the timing of "killer risk" resolution is the second value driver companies should consider when evaluating early R&D projects.

Exhibit 4

DRIVERS OF REAL OPTION VALUE



Managing Real Options Increases the Value of the R&D Portfolio

While option pricing models are indeed the superior valuation tool – the purpose to which the theory is generally put – we further believe that real options can provide a systematic framework that will also serve as a strategic tool. It is in this strategic application that the real power of real options lies.

Option value – unlike asset value (NPV) – is not just "lying there" but has to be extracted proactively by management. One of the advantages of understanding the basic Black-Scholes equation for the pharmaceutical industry is that it identifies the levers that management can apply to maximize option value, such as extending the option's duration through longer patents (e.g., Astra's Losec) or reducing investment to exercise the option through co-marketing agreements (e.g., Pfizer's Lipitor) (Exhibit 4). One such lever, improving the range of expected cash flows, has immediate implications for managing the R&D process and the project portfolio in pharmaceutical companies. It requires the quest for projects with high upsides, accepting the associated risks because management can truncate them.

In circumstances where the uncertainties are resolved over time and management has the flexibility to react accordingly, the value of options increases with uncertainty, flexibility, and learning efficiency (Exhibit 5).

Uncertainty. Higher uncertainty about project value means there is a greater spread between the lowest and the highest possible outcome. Because management has the flexibility to stop developing a project that turns out to be ineffective, the downside risk in the distribution of outcomes can be effectively truncated. This truncation leads to a skewed distribution curve and a shift of the expected value toward higher NPVs. Consequently, managers should select projects with high upsides, even though they may appear to be more risky. Furthermore, if managers have the flexibility to walk away from a project or refine the targeted claims, they should increase the number of high potential early projects, even those with substantial uncertainty (Exhibit 6). Given the same flexibility and similar investment levels due to the tightly regulated R&D process, a strategy built on pursuing riskier projects for larger markets will, in most instances, be more valuable than an explicit niche market strategy.

Exhibit 5

MANAGING REAL OPTION VAUE

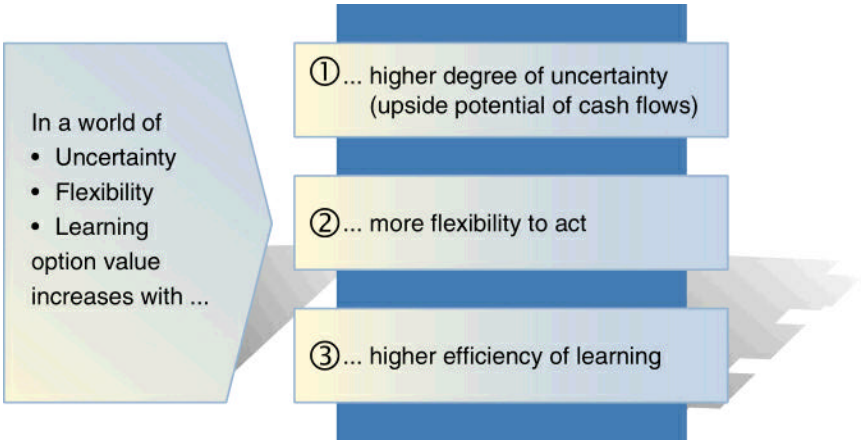
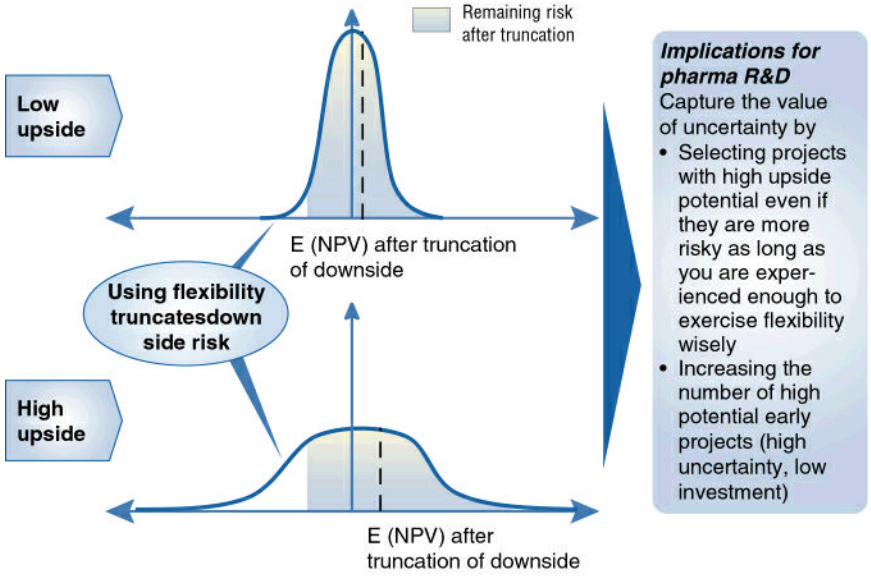


Exhibit 6

VALUE OF UNCERTAINTY

Distribution of outcomes



Of course, the key to any financial project valuation under conditions of uncertainty is a solid estimate of the input parameters. In the long run, structured, computer-aided decision-making – similar to what Merck & Company is reportedly doing – might be justified. Not only does the methodology create value, but using information management systems to incorporate the cumulative learning about the uncertainty of various input parameters also creates value.

Flexibility. High flexibility is the prerequisite for the effective truncation of downside risks. The more decision-making milestones a process has and the faster decision-making is accomplished, the better the attrition of projects can be managed. Here three common pitfalls can be observed: Some companies delay decisions and, in effect, exercise very little flexibility. Others have one extremely rigid decision point (usually the development decision), which thins the project flow so early that there is not much room left for flexibility downstream. Finally, there are companies that emulate the ideal attrition curve almost perfectly, but seem to put more importance on "number of projects per phase" than on "intrinsic project value." None of these approaches is geared toward managing option value as none of them is making wise use of flexibility.

The decision making processes of pharmaceutical companies will have to change. Projects will only be continued if their value surpasses a threshold for the "intrinsic project value" after full learning on investment from the actual development phase. Deviations from development plans and budgets will be evaluated against the added value to the project. Project teams will have to adapt

their initial plans based on latest news from the market or other competitors' learning and remain flexible. The incentive systems will adequately reward an unfortunate team that pushes for killing a project due to new insights.

Learning efficiency. The key to optimizing option value is to resolve "killer risks" early. To improve learning efficiency, managers should focus on three activities:

- Pay for information not for time. That is, tie investments to externally important, value-driving milestones like "oral vs. i.v." The key here is the resolution of uncertainty or, as we might call it, the "learning on investment" rate (LOI). It is a mistake to let internal milestones like the annual portfolio review govern the decision-making, because any no-go decision that is reached before a project milestone serves to negate the investments since the last decision point.
- Strive for maximum incremental resolution of uncertainty at any time, (i.e., do not use "standard development plans" or plan years ahead). Killer risks are not the same in every project, and their sequence is hard to predict. Therefore, go/no-go criteria have to be determined for each project individually.
- Keep your eye on externally available information. A project's value might change dramatically overnight without any new internal information. Any pharmaceutical company should encourage its staff to incorporate changes in external information into their project evaluations and, when appropriate, draw new conclusions.

"Fast followers" in drug development have become extremely adept at learning from their more advanced competitors. They avoid costly mistakes in R&D strategy because their competitors have paid for the learning. Companies can also create value by learning the target profile of competitors before starting Phase III clinical trials. With this knowledge, managers will be better equipped to choose the optimum development strategy for the best relative positioning in the market. We do not suggest that waiting to exercise R&D options is always, or even mostly, favorable. However, given the increasingly unforgiving market, pharmaceutical companies may have to analyze whether the historical rush to the market is the best approach for projects that will not be first in class.

* * *

Option theory enables companies to value their investments not only on the basis of what is known or expected, but also on what is not yet known or what is uncertain. It helps decision-makers identify uncertainties and flexibility and extract inherent option value. It backs management intuition with sound theory and can differentiate between "strategic investment" leading to long-term growth and "wasted money."

* * *

The authors of this article would like to thank Keith Leslie and Phil Keenan for ongoing inspiration.