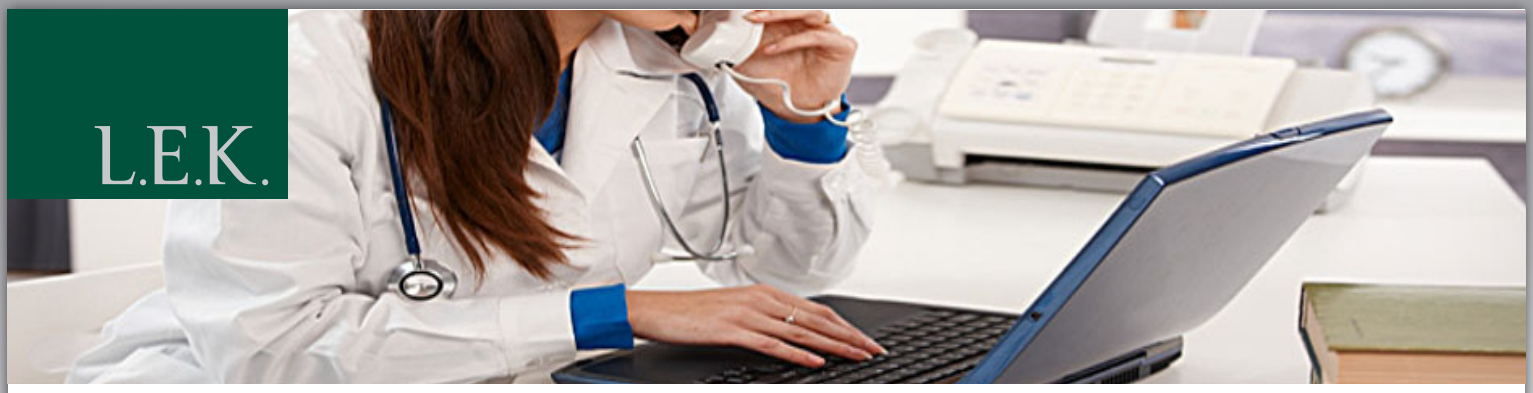


L.E.K.

EXECUTIVE INSIGHTS

VOLUME X, ISSUE 2

Biopharmaceuticals: Enhanced Metrics for Making Clinical Investment Decisions

Properly evaluating clinical program investments is critical for effective portfolio planning, capital allocation, partnering and investing. Traditional approaches reflect the biopharmaceutical industry's historic focus on large, blockbuster products that typically target one major clinical indication. Approaches such as optimizing the trade-off between the cumulative probability of success of a program against the value of the product, if successful, introduce biases that favor large, blockbuster programs over small, niche programs with potential application across multiple disease indications.

In this issue of L.E.K. Executive Insights *we introduce metrics that minimize this bias and level the playing field, allowing managers and investors to make apples-to-apples comparisons of clinical-stage biopharmaceutical programs with very different risk/reward profiles.*

The biopharmaceutical industry has traditionally based its livelihood on blockbuster drugs that target large, chronic disease markets, but recent setbacks have raised questions about the sustainability of this model. At the same time, specialty pharmaceutical companies have carved out profitable niches by targeting smaller indications with lower potential revenue, and consequently they have avoided competing head-on with large pharmaceutical companies.

Recently, large companies have taken a keen interest in specialty markets as a result of a number of favorable factors. Many of these specialty markets require smaller clinical investments due to smaller clinical trials, and they generally have different safety hurdles for approval than the more traditional, chronic, primary care disease indications. In addition, they require smaller sales forces to reach their more concentrated prescriber base. Products targeting these markets may also take less time to go from research to commercialization, and those that target certain indications may be eligible for fast-track designation, orphan drug status, or priority review.

To properly evaluate the potential of specialty drugs, pharmaceutical executives must account not only for diversification of product franchises but also for indications within individual products. The reason: Some specialty products (e.g., oncology, anti-infective, and immune-mediated biopharmaceutical drugs) have demonstrated applicability across multiple disorders and diseases.

Managers must properly evaluate these product investments for effective portfolio planning, capital allocation, partnering and investing. This L.E.K. *Executive Insights* article will introduce improved metrics that more accurately reflect the opportunity cost of alternative investments as well as the potential value from diversification and the creation of multiple real options.

Biopharmaceuticals: Enhanced Metrics for Making Clinical Investment Decisions was written by **Pierre Jacquet,** Vice President, and **Troy Norris,** former Vice President, L.E.K. Consulting, and **Joe Walsmith,** Director, Life Sciences Business Intelligence, L.E.K. Consulting. Please contact L.E.K. at lifesciences@lek.com for additional information.

The Traditional Approach

Most methods for evaluating biopharmaceutical drugs assume linear development paths that result in clear success or failure outcomes. This approach is appropriate for many drug candidates targeting chronic, primary care disease markets where future revenues depend on a single blockbuster indication. However, these approaches are not well suited for assessing the value of products with potential application across multiple indications or with the potential for accelerated development and commercialization.

Portfolio planners typically weigh clinical risk against NPV to determine their drug development strategy. Generally speaking, products with a high NPV and probability of success represent the ideal investments, with most companies aiming for a balanced portfolio of high-risk/high-reward and low-risk/low-reward products. However, by focusing on single lead indications with clear yes/no outcomes, program evaluations are biased toward large, "all or nothing" bets.

Furthermore, when portfolio planners are faced with programs targeting smaller indications, they may undervalue them by using traditional metrics. These metrics often place disproportionate value on high-NPV products, and consequently they tend to undervalue companies that pursue specialty markets with smaller investments and potentially higher internal rates of return (IRR). But as the pharmaceutical industry increases investments in specialty products, managers must find new ways to evaluate these companies and their drugs. Companies looking to diversify risk and maximize return with a lean portfolio of products have increasingly been pursuing products with potential use in more than one indication. To illustrate the value-creating potential for such products, we will discuss enhanced valuation metrics and a simulation approach based on Monte Carlo analysis, to enable apples-to-apples comparisons of clinical programs with very different risk/reward profiles.

Enhanced Evaluation Metrics

We will compare a traditional, large chronic disease program with a targeted anti-cancer program. Figure 1 summarizes the similarities and differences among the two products studied. Each drug was developed and commercialized by leading pharmaceutical companies and approved in the U.S. between 1996 and 2003. Each product was expected to achieve blockbuster status with peak revenue of more than $1 billion.

Opportunity Cost of Investment. Individual oncology and specialty therapeutics with applicability across a variety of cancer indications often realize lower total peak revenues than traditional chronic drugs. However, oncology products generally require less time and investment to reach the market. Therefore, managers can use more sophisticated metrics to reflect these differences and to avoid undervaluing programs targeting multiple smaller indications. To determine the attractiveness of an oncology or other specialty biopharmaceutical product investment, managers must compare the value created through each stage

Figure 1

Products Studied: Traditional Chronic Disease Drug vs. Targeted Anti-Cancer Drug

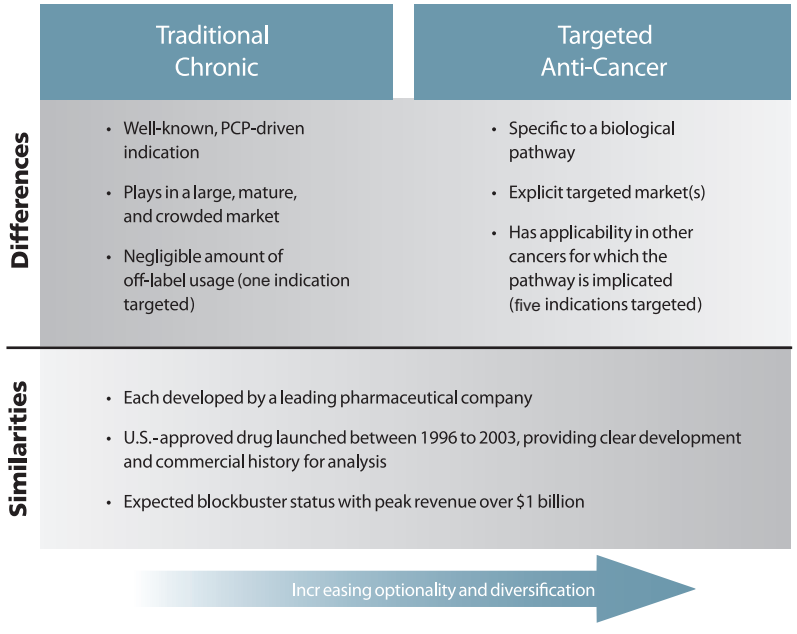
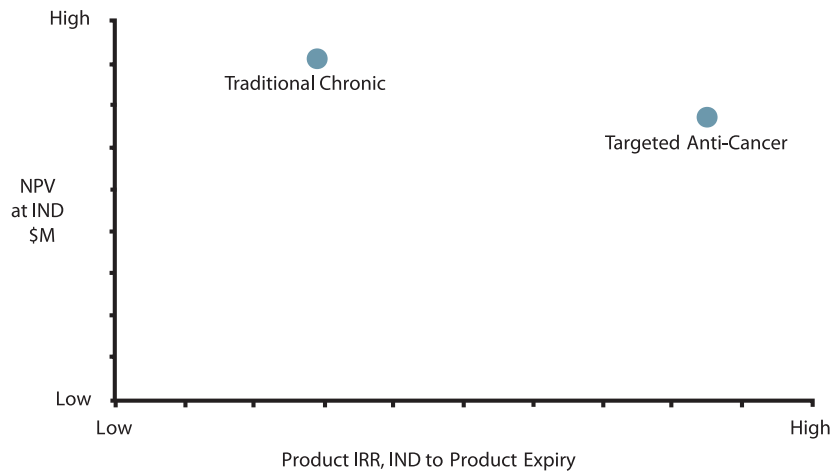


Figure 2

Product NPV vs. Internal Rate of Return (IRR)
Note: IND = Investigational New Drug



of development to the opportunity cost of the relative amount of incremental investment in the program. Although oncology programs typically have a lower NPV upon initiation of clinical trials (i.e., at IND stage), they appear more attractive when using return on investment relative to the opportunity cost of investment. For example, in Figure 2, the targeted anti-cancer drug requires only about one-third of the clinical investment of the traditional chronic drug to reach roughly the same expected NPV, giving the program a significantly higher IRR.

Another useful metric for evaluating relative value creation at each development stage is the ratio of expected NPV per dollar of clinical investment, as shown in Figure 3.

Since clinical development investments are made in phases, this measure of return can help managers prioritize near-term investments in clinical trials and manufacturing. Furthermore, the relative return on investment over the course of development can help determine the optimal time to in-license or out-license clinical candidates in order to maximize value. For example, when studied from an incremental IRR perspective, Phase II clinical proof-of-concept trials typically provide significant return on investment. Therefore, it often makes economic sense to take a product through Phase II proof-of-concept before partnering it to a large company with R&D and commercial capacity. Large companies can often achieve a higher return on investment in Phase III than smaller companies because their net incremental investment is lower on the margin. This reinforces the utility of using metrics such as IRR and investment-indexed expected NPV to evaluate clinical programs for effective portfolio planning, capital allocation, partnering, and investing.

Still, while metrics such as IRR and investment-indexed expected NPV offer additional value by accounting for the relative investment of dollars, resources, and time, it is critical to consider the potential upside from downstream option-creation when making clinical investment decisions in programs with applicability across a variety of disease indications.

Figure 3

Incremental Expected NPV and Clinical Investment by Phase

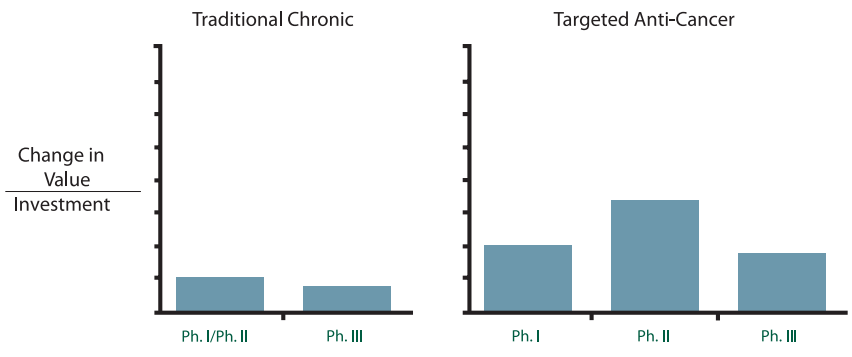
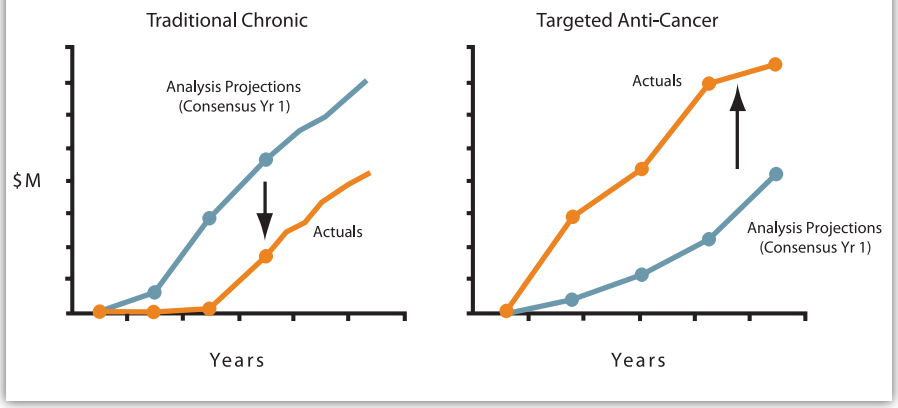


Figure 4

Actual Sales History vs. Analyst Projections over Time



Diversification and Option-Creation. Standard metrics for evaluating clinical programs tend to understate the potential upside from downstream option-creation, as well as the magnitude of downside risk that could reduce commercial value and impact launch timing but not overall probability of success.

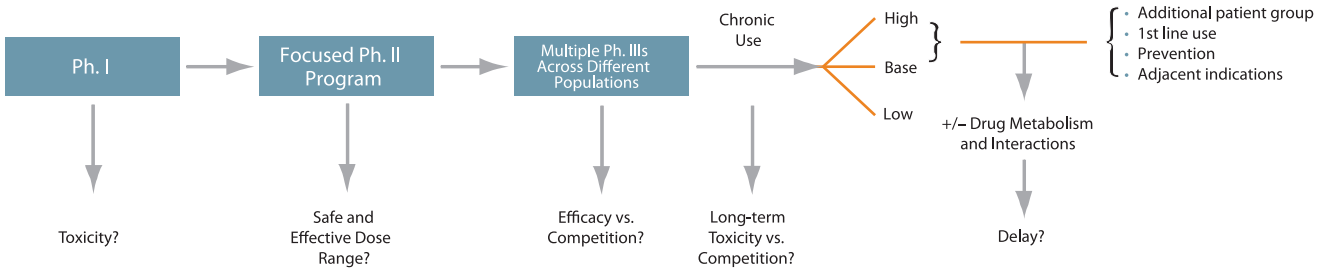
Consequently, the performance of specialty therapeutics with applicability across multiple indications has historically been underestimated.On the other hand, traditional chronic-disease drugs often perform below analyst expectations, which typically do not account for all the downside risks in a single-indication product. Furthermore, by focusing on the probability of success, analysts understate the risk of delays, labeling constraints, and other potential factors that could reduce commercial success.

Figure 4 illustrates the gap between analyst expectations and actual performance for the two reference drugs that we analyzed. In looking at a broader set of examples, we found a clear pattern: The potential for traditional chronic disease therapies targeting large markets is typically overestimated, while the option creation in oncology and other specialty markets is underestimated.

To address this disparity, we first characterize the differences in development paths between each type of clinical program. As shown in Figure 5, most development programs are linear with significant increasing investments and clear decision-points leading to large potential rewards if successful. Risk-adjusted values for this type of serial, linear decision-path can be estimated using discrete probabilities of success at each stage.

Figure 5

Typical Linear Development Path for Traditional Chronic Disease Therapies



In comparison, some oncology and other clinical candidates have significant option-creation and represent a diversified portfolio of investments across multiple indications, as shown in Figure 6. These development paths are characterized by multiple, smaller investments with lower rewards, as well as a plethora of loosely linked decision points. Because multiple indications can be studied in parallel tracks, a probability distribution of potential outcomes exists, one that narrows over the course of development.

Products with significant potential for option-creation provide some degree of diversification of the clinical investment risk. To the extent that results in alternative indications are uncorrelated, the clinical candidate may have a high probability of achieving success in one or more indications, even if the probability of success in any single indication is low. Targeted therapeutics may also increase the probability of success in a narrower set of indications.

Enhanced Program Evaluation Metrics

To illustrate the applicability of enhanced program evaluation metrics, L.E.K. analyzed a number of clinical programs with differing attributes. For example, we compared clinical candidates targeting a single large, chronic, blockbuster market with cancer products targeting multiple indications in parallel. Based on this analysis, we have developed metrics for evaluating and prioritizing clinical candidates – metrics that more accurately reflect the opportunity cost of alternative investments and the potential value from diversification across indications.

For example, the risk-adjusted internal rate of return for a program, which accounts for the relative size of the investment, should be used with expected net present value (NPV), the traditional measure of total value creation. Similarly, the change in value from successfully completing a clinical study can be indexed to the cost of performing the study, to compare relative returns on investment for alternative near-term clinical programs.

Standard metrics tend to understate the upside potential from downstream option-creation for clinical programs. They also understate the downside risks that can reduce the financial return on a drug and change the timing of its launch but not the overall probability of success. Products with applicability across multiple indications have a more diverse clinical investment risk because they spread the risk across a number of opportunities. That increases the chance that the program will generate some returns rather than betting on a single all-or-nothing outcome. As a result, some programs with multiple smaller indications may have a lower overall expected value but a significantly greater probability of achieving a positive NPV. Monte-Carlo simulations of outcome distributions for these clinical programs enable apples-to-apples comparisons of clinical programs with very different risk/reward profiles.

Figure 6

Typical Parallel Development Path for Cancer Therapies

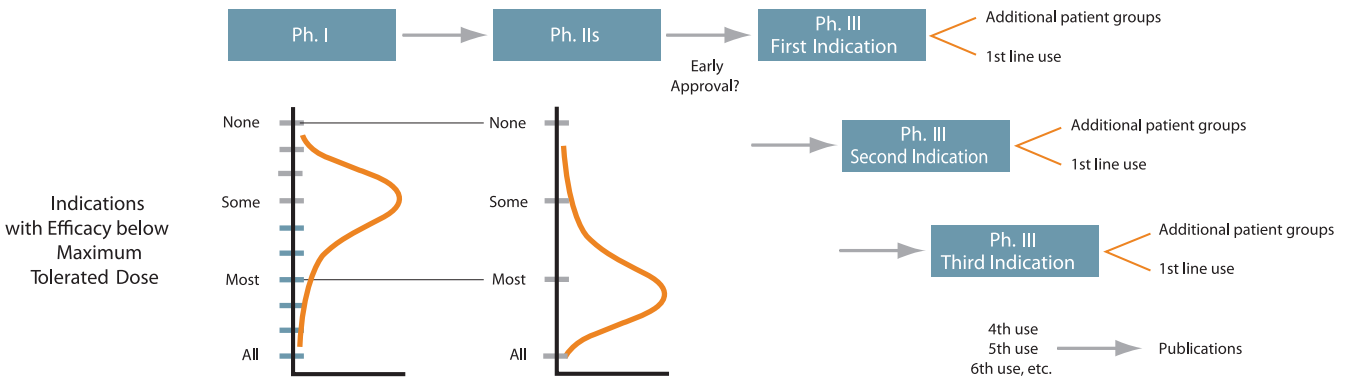
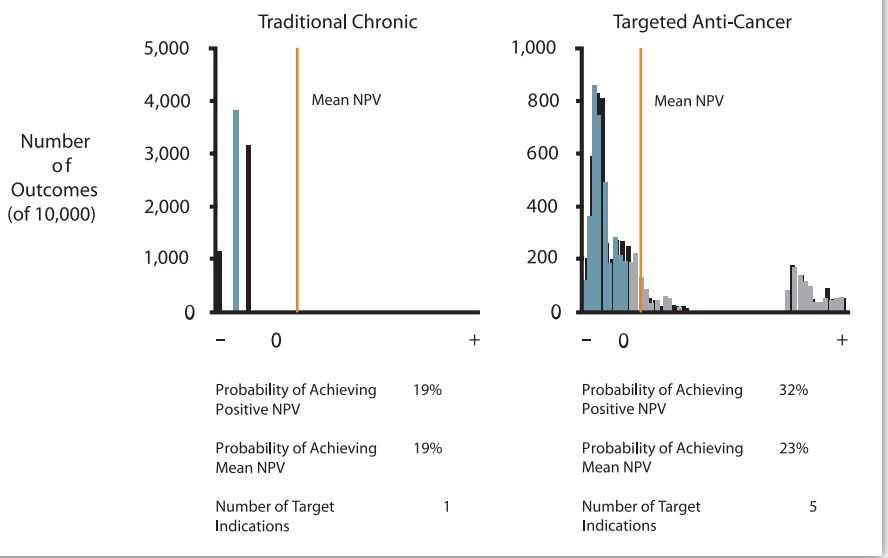


Figure 7

Distribution of Potential NPV Outcomes



Because simple success probabilities and decision-tree analyses on an indication-by-indication basis do not capture these effects, the traditional valuation approach will understate the intrinsic value of a program with multiple, diverse indications. Instead, the full distribution of potential outcomes across the portfolio of clinical indications needs to be simulated, as shown in Figure 7. Here we can see that the traditional chronic drug has only a few potential all-or-nothing outcomes. In contrast, the targeted anti-cancer drug has a broad range of potential outcomes that reflect diversification across clinical indications. Although the targeted anti-cancer drug with multiple smaller indications has a lower overall expected value, as shown in Figure 2 (page 3), diversification leads to a significantly greater chance of achieving a positive-NPV outcome, as shown in Figure 7.

Therefore,when making investment decisions, managers should consider the distribution of returns from the aggregate portfolio of potential indications for products with significant option-creation. Individual oncology indications – though representing low expected NPV and a relatively low probability of success at IND – result in a favorable success probability at IND when considered as a portfolio. In contrast, the traditional chronic drug does not benefit from these portfolio effects because it is generally targeted at a single indication.

Diversification and option-creation should be considered when making clinical investment decisions.

Portfolio Planning and Capital Allocation

Standard program evaluation metrics tend to underestimate the upside potential of products with broad applicability across multiple indications, as well as the cumulative impact of multiple downside risks in otherwise straightforward development programs. As traditional, chronic blockbuster markets have become more competitive with reduced unmet need, the downside risks of product delays, withdrawals, or restricted labeling have increased significantly and need to be explicitly modeled by portfolio planners.

Partnering

Partners should explore ways to maximize and share the option value of programs. For example,this can be accomplished by retaining or sharing indication specific rights, in many cases, with cross-payments of milestones and royalties. Similarly, co-promotion arrangements by indication, and/or having the more mature commercial partner create a sales infrastructure for the licensor to promote into retained indications, can maximize this option value for the relationship. Lastly, increasing use of tiered royalty arrangements and/or milestones tied to sales thresholds can reward the innovator while protecting the licensee against downside risks.

Investing

Capital markets may undervalue products with significant optionality, creating arbitrage opportunities for sophisticated investors. Targeted medicines have less diversification than traditional cytotoxics in the case of anti-cancer drugs, or broad-spectrum antibiotics in the case of anti-infective drugs, but should have lower risk overall due to more targeted (less toxic) and better-validated biology. Targeted medicines may also create real options resulting from application across multiple indications with a common biological basis (e.g., the use of Rituxan, a targeted oncology product, used to treat rheumatoid arthritis).

Conclusion

By being equipped with sophisticated and flexible metrics to evaluate clinical investment opportunities, managers and investors can better evaluate products that may, at first, appear to be unfavorable using traditional metrics. Furthermore, employing simulation analyses to address the complexities of concurrent development paths can help managers to identify optimal strategic choices. Finally, as investors and managers look to maximize future revenues and shareholder value with the least amount of risk, these new tools for portfolio planning and evaluation can help to identify opportunities and potential pitfalls where standard metrics have fallen short.