PORTFOLIO MANAGEMENT IN PHARMACEUTICAL/BIOTECHNOLOGY R&D

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Introduction

The goal of effective portfolio management in a pharmaceutical or biotechnology research and development program is to maximize return on the company's R&D dollar. Easily said, but how do you accomplish this?

The process begins with a strategic market analysis. This reveals opportunities for the development of new diagnostic or therapeutic products. Then, R&D proposals are generated, and sifted through a screening step using simple, nondemanding models to determine minimal acceptability according to predetermined criteria. Next, the surviving proposals are subjected to a more detailed selection methodology usually involving both qualitative and quantitative measures. Then, risk and return are examined in rigorous (but rigid) assessment models such as net present value (NPV), and previously selected proposals and existing projects that do not meet corporate goals are weeded out. Finally, portfolio analysis and budget allocation models are used to prioritize and choose between the good projects to achieve the best possible overall combination. This process, complex and iterative in nature, is carried out differently at each company.

This is complicated and expensive. How do we justify such an elaborate procedure? Almost everyone in the industry would probably agree that the R&D environment is becoming steadily harsher. Over the decade of the 1980s, the cost of developing new drugs rose about 50% faster than sales, while the number of new chemical entities launched remained more or less constant from year to year.[3]

Cronrath, *et al.* have pointed out that;

> "...there is only one way to avoid subcritical mass in research and development - focus on those few core therapeutic areas where the company has the greatest strengths and market opportunities."

The questions now are, how do you focus on the best opportunities? What methodologies and models will help you make better and faster decisions about the use of your scarce resources? In this paper, I propose an integrated approach using different models in each phase of the research and development process.

Strategic Market Analysis

The process of portfolio management begins with a strategic market analysis. This is best done explicitly and systematically. It is recommended that you address this need head on.

Market Niche Analysis

The analyst examines the market (diagnostic or therapeutic needs) and assesses the existing products in terms of unmet medical need. She or he then considers the existing company product line and products in development or research. Market gaps or niches are identified that suggest leads for future R&D. The concepts of market segmentation and product differentiation are both used to converge upon a list of identified market niches and the potential products to till them, working each concept alternately towards the final result.

Market Model

A marketing model, such as that developed in the early 1980s at Ciba-Geigy, uses a flowchart to describe the interfaces and information flows between a treatment market model, market share model and sales model. The combined models are used primarily to forecast raw material requirements. In the same years, a similar model was used at Syntex to forecast raw material demand. Simpler versions could be used at earlier stages in the development cycle to help make project selection and investment decisions.

Multiple-Factor Matrices

Multiple-factor matrices have been used by pharmaceutical companies to help determine the general market attractiveness of various indications (medical conditions) and objectively evaluate the general competitive position of proposed or existing products. A technique used at Boehringer Mannheim is referred to as portfolio analysis.[3] It includes a first-stage matrix showing Main Portfolio on the horizontal axis versus Market Attractiveness on the vertical. A diagonal line divides the matrix into two zones, "promising' and "dangerous". Subportfolios are plotted, and then broken out into matrices of their own, with specific products plotted versus specific competitive position. For a very large company with many products, another layer could be developed, making it a three-level hierarchy of matrices. Matrix analyses are valuable primarily because they enable

the analyst to display several or even many products rated according to their position on two attribute scales. The matrix is easy to prepare and understand. It is the clearest and most concise way to show a mass of data of this sort, although it is worth pointing out that the actual data content is no different than a table with products on the vertical axis and two rows of figures (values). The simplicity and visual appeal of the matrix should not blind us to its limitations, which include the relative paucity of actual "data" presented.

Research Survey

Some years ago at Searle, a formally structured interview technique, the "research survey", was used to "integrate external technologies and market needs with internal competence". This technique used Searle scientists as interviewers of investigators in clinical settings, with the purpose "to provide, through validation from external sources, a justification for the initiation of a research project'. At least initially, this technique "exceeded expectations''.[10] In the early 1980s, a similar idea was used at Syntex, with mixed results.

Screening and Selection Models

The first stage in selection of research and development projects for investment is a quick triage screening for acceptability. Proposals are sorted into the triage categories of "yes" (acceptable), "maybe" (questionable) and "no" (not acceptable).

To carry out the triage separation, a quick qualitative feasibility analysis covering each relevant area is run on each project. Areas to look at might include scientific, technological, medical, regulatory, patent or licensing rights, marketing, production and distribution, and financial. Besides theoretical feasibility, the company's actual capability in each critical area must be assessed. This brief qualitative assessment may be accompanied by a simplified quantitative model such as one of those suggested below.

After triage, nothing further is done with the proposals in the "no" category. Focus is now on the "yes" category, which will be put through further, more rigorous, detailed and quantitative evaluations. The "maybe" projects are set aside. These projects will be reassessed only if the "yes" category doesn't yield enough projects to meet our predetermined need. This is not a likely event in most organizations, where good ideas usually far outrun resources.

Checklists

A simple, very popular and probably the oldest screening method is the checklist. A list of success criteria is drawn up, usually in consultation with all the decision-makers and key decision-influencers. Buy-in to this list is essential; everyone must agree that the list includes all (and only) the relevant and important success factors. Projects are then checked against each success criterion, usually being rated simply as acceptable or unacceptable on each. Checklist models are easy to understand and use. They provide a formal approach to the screening process without requiring the development of a lot of detailed information and undergoing a significant planning effort.[7]

Hurdle Rates

The hurdle rate is one of the oldest screening techniques. It requires a prior assessment of the project's costs and return on investment. The return on investment (ROI), usually expressed as an internal rate of return (IRR) is then compared to the predetermined minimum acceptable rate, the hurdle rate. The apparent simplicity of this approach disguises the considerable amount of work that has to be done ahead of time if the comparison is to have any validity.

Scoring Models

Scoring models are typified by the "Innovation Potential" model developed by Paolini and Glaser.[5] The process begins with a checklist of success factors, carefully chosen to represent what is most significant for the specific company. Each factor is given a weight, based on the significance of that factor in the specific company environment. Each project is then scored on each factor, the score multiplied by the weight, and the total score used to compare proposals against each other. A cutoff level is predetermined, and projects not reaching the cutoff value are dropped from further consideration.

Profile Models

In a profile model, projects are subjectively but quantitative y rated to facilitate comparison. Various subjective project criteria are developed and listed, with a numeric scale for the ratings. The scale is often displayed with negative (undesirable) and positive (desirable) regions left and right of the neutral zero rating in the center. Each project is then subjectively rated by plotting data points as in a scattergram. When the data points are connected with lines, a visual "profile" of the project emerges.

The visual display is especially useful when there area lot of projects being compared, each one having been scored on a lengthy list of attributes. The profile can be thought of as a visually-enhanced scoring model.

Index Models

Being quantitative in nature, index models depend on a bit more work up front than the simple checklist and scoring models. A typical index model is the benefit/cost ratio, which uses factors such as return on investment from R&D, or even present value of expected future benefits as the numerator. R&D costs or expected future costs appear in the denominator.[7] Thus, the modeller must develop at least a sketchy project plan and ROI analysis.

The best of the index models is the profitability index. It can be very useful in comparing the value of various developmental research projects involving new therapeutic approaches, each one having a handful of potential lead new chemical entities (NCEs). The best version of the profitability index uses net present value (NPV) as the numerator and discounted investment cash flow as the denominator. The resultant index number is strongly influenced by the size of the investment, thereby providing a measure of project magnitude that is lacking in straight NPV or IRR.

Expected Value Analysis

The expected value concept can be of enormous value to the decision maker in selecting projects.[4] It is assumed that rational decision makers will select those projects having the highest expected value scores. Expected value is a way of recognizing the uncertain nature of the estimates that go into the cost and benefit inputs of a ROI analysis. The estimates are given as a range of possible values. This range could be the three estimates of PERT (program evaluation and review technique), or a full range of values defining a function curve, as in Markov simulation analysis. In any case, a probability is associated with each estimate and the product of the two is the expected value.

Risk Analysis Models

Most risk analysis models make extensive use of the expected value concept. Souder discusses a model that starts with a complete set of payoffs, each one with a subjective estimate of its probability of occurrence. These payoff-probability points are then plotted to develop a risk-return curve. The curve graphically describes the upside potential, the downside risk and the degree of tightness around the most likely value (which can be loosely thought of as the degree of certainty of achieving the most likely result or a value close to it). This expected value curve can then be graphically compared to that of another project, and selection made based on a detailed analysis. Discussion of these curves by the decision makers will bring out the existence of risk-averter and gambler strategies and facilitate a more informed decision?

This is all well and good, but what about those original estimates? Are they any good? One answer is that a full risk-return curve is probably much more accurate, and certainly less misleading than a single value. As Allen says, "The advantage of using subjective probabilities as a means of expressing opinions about uncertain situations is not that the numbers have any objective reality (which they do not), but that they enable the consequences of those opinions to be explored logically and rationally."[1]

Risk and Return Assessment Models

Once you have tentatively selected your projects using one or more of the selection models outlined above, it is essential to subject each project to a full assessment of risk and return. The planning requirement becomes burdensome now, you no longer can proceed with simple single subjective estimates of cost, probability of success and return. Each project must have at least a preliminary project plan, as well as a rigorous risk assessment. At this point, it is usually helpful to return to the basic facts that got you interested in the project in the first place; the market and feasibility analyses. These analyses should be updated and expanded greatly in detail. When the preliminary project plan and risk assessment is complete, you are ready to calculate return on investment (ROI) and make budget allocation and other portfolio management decisions.

Payback

Possibly the oldest and certainly the simplest of ROI methods is payback. It remains popular, but the inputs being used today are generally far more sophisticated than they were a decade or so ago. The payback concept is time-related; that is, success of the project is measured in terms of the time required to "pay back" the investment. If return is measured crudely, such as by gross profits (or even worse, gross sales), payback is a crude and misleading instrument indeed. However, if net profit, after all costs are deducted is used, and the figures are then discounted in a net present value analysis, payback can be converted into a relatively sophisticated measure. It still lacks some of the dimensions that are useful in making budget allocation and go-no go decisions. For one thing, it gives no clue as to the magnitude of effort required, nor does it provide information on the per-dollar return on investment. All it really provides is an "investment dollar turnover period", or measure of cycle time. Because of this, it probably has more applicability in diagnostics rather than therapeutics.

Net Present Value (NPV)

Net present value (NPV) has long been considered the intellectually most defensible measure of ROI. NPV is based on the concept of the time value of money, using a discount or "negative interest rate". The discounting is compounded annually. One of the key factors in any NPV analysis is the choice of discount rate. The higher the rate, the smaller the present value.

When selecting the appropriate discount rate, you have to take several factors into account. First is the basic, long-run "time value of money" or interest rate, of about 2%. To cover inflation, add another 3%, for a total of 5% currently. Most discounters use a considerably higher rate. Why? Because they are adding in a third factor, investment uncertainty, or risk. This is a poorly-thought-out practice and not the right way to account for project risk, but practically everyone does it. The risk element should be kept out of your discount rate as much as possible, it can be dealt with explicitly through rigorous risk identification and assessment.

The procedure for doing an NPV analysis is simplicity itself. The general method is to multiply the value of the future dollars by a discount factor (a unique factor, always less than 1.0, for each year). For an example, the present value (PV) of $5, to be received (or paid) one year from today, and discounted at 10%, is approximately $4.54 (5 x 0.909). The PV of $5.00 at the end of 2 years is $4.13 (5 x .0826). The factors are readily available in published tables, but you need go no further than your pocket calculator, which probably has a NPV function built into its logic chip, requiring only that you enter the desired discount rate and dollar amount for each time period.

So, now you have done your NPV analysis and you have your answer, something like "Project Z has a NPV of $5.4 million". What does this mean? The theorists will tell you that ANY positive level of NPV is a signal to approve the project, and any negative NPV is a signal to disapprove. Everyone else, of course, finds this exasperating y theoretical, and they get nervous unless the NPV is significantly large by whatever private mental standard they are using to judge its magnitude. This leads to a problem with NPV; people try to compare the NPVs of different projects directly. This is not a wholly defensible procedure. For one reason, it gives a distorted answer to the question of relative project magnitudes alluded to above. To compare projects of greatly differing magnitudes, use the profitability index with NPV as the numerator and discounted cost cash flow as the denominator.

NPV analysis handles uneven cash flows very nicely - and it is the only ROI technique that does this. Since uneven cash flows (over time) are the rule in our industries, this is a major consideration for pharmaceutical and biotechnology R&D portfolio managers. NPV is also the only good way to compare projects that have greatly differing durations and timings (that are in the different phases of their project life cycles).

Internal Rate of Return (IRR)

IRR is the inverse of NPV; it is the discount rate required to make your positive (profit) and negative (cost) streams exactly cancel each other out and yield a NPV of zero. IRR sounds like a simple interest rate when statements such as "Project A has a IRR of 19.5%" are made. For this reason it is extremely popular with accountants and other financial types. Venture capitalists, investment bankers and stock analysts are more skeptical, being very aware of how much can be hidden behind that one simple number.

Outward simplicity is the main problem with IRR. NPV at least challenges most people to ask more questions and find out what it is based upon; IRR tends to short-circuit the communication process because it sounds so certain and final. Also, even more than NPV, IRR gives no hint at all, concerning the magnitude of the project. However, in spite of these disadvantages, an IRR analysis is very important to assure top management and investors that you have performed a financial analysis that enables them to compare the "total worth" with the return from alternative investments the firm could make. Don't let the apparent simplicity of IRR lead to invidious comparisons against returns potentially available from investments outside our industry' these comparisons are appropriate only if the company is considering divesting itself of its future in pharmaceuticals or biotechnology.

Simulation Modeling

The simulation technique is not limited to PERT, of course. Simulation can be used to model the uncertainies inherent in all the relevant factors bearing on project estimates, such as the marketing inputs.

The analytical process involves three steps. First you estimate the range of values for each of the factors being modeled. Software programs are available to help you with this, wherein all you need to do is select a probability distribution that you feel best models the probable distribution curve of your data element. Next, you select at random from the distribution of values, one particular value for each factor. Then combine the values for all the factors and compute the

NPV (or IRR) from that combination. Again, there are software programs available to enable you to do this in an instant. The program then does this over and over again to define and evaluate the chances of occurrence of each unique combination of factor values (each unique value of the rate of return). Usually about 300 runs, taking a few seconds, will give you a reliable result.

The principle value of this technique is to refine your estimates and the resultant ROI in cases where it is essential to obtain the best possible answers. This implies that the project in question is large and lengthy, its success is of great importance to the company, and the downside risk potential is significant; a good description of the typical pharmaceutical or biotechnology project!

Budget Allocation and Portfolio Analysis Models

Once you have screened, selected and assessed your projects, you are finally ready to make the "final" selection to make up the best possible package or portfolio to fit your company's R&D budget. The models discussed below are useful for prioritizing and choosing between "good" projects.

Portfolio Analysis (Budget Limits)

Classic portfolio analysis is a technique developed by financial analysts concerned with maximizing return from a portfolio of financial investment instruments such as common stocks, industrial bonds or tax-exempt securities. The portfolio analysis model assumes that there are discrete alternative funding levels available for each project. This is rarely true of our industries' projects, but there might be occasions where management is trying to decide which projects to speed up and which to slow down or halt, in order to maximize overall return.

The principal value of the portfolio analysis model is to determine the appropriate budget funding levels for your projects in the next fiscal year. To use the model, you must first decide which discrete alternative funding levels you will consider for each project, and calculate the projected return for each combination of project and funding level. This is a massive task if it is to he done realistically, because there are as many possible combinations of tasks as different funding levels (spending rates). Furthermore, many tasks, such as contract toxicology studies, do not have much flexibility in spending rates. I could conceive of some potential usefulness for this model in deciding funding levels for entire research categories, but not for individual projects.

If you were to use this technique for allocating funds between therapeutic areas, for example, you might proceed as follows. First select your proposal array of discrete funding levels, and show them in a column to the left of a two-factor matrix, as shown in the example. These are the labels for each row of the matrix. The therapeutic areas are arrayed on the horizontal axis, forming the labels for each matrix column. The expected value resulting from the planned efforts in each therapeutic area is shown in the appropriate cell. Totals across therapeutic areas for each discrete funding level are shown in a payoff column to the right of the matrix. Obviously this is a very crude model for our purposes, since it is limited to considering the same discrete funding level for all therapeutic areas in order to establish a combination for totaling (each row in the example used).

In theory, a portfolio analysis model could help you decide whether or not to purposely fund some areas at their lowest reasonable level, or to completely reject further work in other areas in order to concentrate the limited funding available on the therapeutic areas most likely to pay off with the highest IRR or NPV. However, this concept has so far had very limited use in any industry (outside the financial area). A similar risk management and evaluation model has been used with success in the motion picture business.[4]

Souder states that "there is an emerging position that portfolio models should not be used strictly for their analytical capabilities. Rather, the models should be used for their organizational behavior impacts, and to facilitate improved organizational decision making. The few successful applications...reported in the literature have all stressed these decision process benefits, rather than the correctness of the model's outputs."[7]

Pairwise Comparison by Forced Choice

This method uses personal utility theory to set up decision frameworks. It incorporates corporate values (goals) which have already been accepted as valid. The goals are compared to each other in pairs and assigned weights, in an explicit tradeoff process. The same process is repeated for each project and goal pair, then the results are multiplied and summed as overall project scores. The scores are then used to determine project budget allocations. Themethodology is complex and space does not allow adequate treatment herein.[8]

Inputs and Outputs

Input Estimates

The relevance, completeness, accuracy and precision of input estimates constitutes one of the most crucial of the inherent limitations of management models in

the portfolio management process. There are many ways to improve the estimates you receive, but that topic is outside the scope of this paper. You should prepare a detailed work breakdown structure (WBS) to help improve the task estimates. A careful strategic market analysis, including the crafting of a claims structure and complete product profile will greatly improve the market estimates.

Model Output

The biggest problem with output from the models is that it is too often taken too literally. I am reminded of what Rowe had to say on this issue. He pointed out that an estimate, once made by anyone considered to be an expert, is usually accepted as fact. It is then widely promulgated as fact, without any of the estimator's original caveats or qualifications.[6]

The entire problem is summed up in the popular aphorism "GIGO", which stands for "garbage in - gospel out".

Sensitivity Analysis

Sensitivity analysis is a very useful technique to deal with the consequences of uncertain y in your input estimates. Sensitivity y analysis should always be run on any input factor (independent variable) that you suspect may have a significant impact on the output (dependent variable), such as NPV or IRR. Simply vary the input factor by a percentage that you think might result in a significant change in the output. You should start by "bracketing" the original estimate widely (picking input values much higher and lower) so as to quickly home in on the sensitive zone. With NPV, it is a good idea to find out what value of the selected input variable results in a reduction of NPV to zero, or negative. With IRR, you can find what input value results in just making the hurdle rate.

The point of this exercise, (which by the way is very easy to do in this day of spreadsheet software), is to find out which estimates have the most profound effect on the bottom line, and at what point does the result become critical. This enables you to go back to the estimator and ask for re-evaluation in light of the effect that variations in the estimate has on the results. this will pinpoint weaknesses in the estimation effort and point to where you can best spend your limited dollars on research to improve the estimate.

Human Relations and Limits on Use of Models

Buy-in

All the sophisticated models and estimation effort in the world will do you little good unless you get all the decision makers and relevant decision influencers to buy in on them, on your efforts, and on your results.

The Model World and the Real World

All of the analytical models discussed above have severe inadequacies in meeting the human needs of project and portfolio management. Souder makes a case for the real world environment, as contrasted to an implicit "management science viewpoint". For example, in the real world organization, many decision makers and decision influencers are involved in a dynamic (sometimes chaotic) environment; as opposed to the "model" viewpoint of a single decision maker in a well-behaved environment. Goals, information, consequences, independence or interdependence of projects are all similarly treated. In the model world, the best portfolio of projects is decided strictly on economic grounds, whereas in the real world, satisfactory portfolios may possess many non-economic characteristics. In general, organizational behavior needs must be satisfied before any project evaluation model can be used effectively. Organizational goals and constraints at all levels in the organization must be clearly defined and agreed upon. All the parties involved need to understand what types of projects are acceptable and how their proposals will be judged.

Most project evaluation data are necessarily subjective and a spirit of trust and openness is needed for full and open exchange of data and information. Each party needs to appreciate the larger needs of the organization and be able to comprehend, empathize with and come to consensus with each other. All parties must have a depth of factual knowledge about the projects and their environment, as well as complete awareness of their feelings.[7]

Conclusion: A Proposed Integrated Approach

In conclusion, I would like to propose to you an overall model for your portfolio management process: an integrated approach applicable at any phase of the project life cycle.

Basic Research Phase

In the basic research phase, when you are still searching for a lead compound, diagnostic method, or approach to a genetic engineering problem, it is most valuable to spend effort on strategic and market analysis. Screening models should be used to separate the losers from the potential winners and runners-up.

Exploratory Research Phase

Selection models and simple assessment models are useful to continue the project selection process. Probability trees and other decision analysis models can be used to solve difficult decisions and home in on key parameters for further study. Full risk identification and analysis should be done.

Development Phase

During the development phase, it is critical to perform full-scale return on investment (ROI) evaluation analyses, if this hasn't been done previously. During this phase, project effort is greatly expanded and the rate of spending is very fast. Risk events, if they occur, will have their greatest impact now, as there is already much at stake (sunk costs are mounting fast). Decision points become important, and decision analysis techniques, which are outside the scope of this paper, become important as knowledge of the project expands and estimators are capable of greater accuracy and precision.

All Phases

During all phases of research and development in our industries, it is of critical importance to pay close attention to the budget allocation process. Whether or not you are using an explicit allocation model, there are implicit decisions being made that become apparent in the resulting budget. Decision analysis models are also useful at all stages, although the questions put to them vary greatly. ROI techniques are obviously important throughout the life cycle of the project. Risk assessment and response planning is always critical. Finally, sensitivity analysis is of great usefulness in testing the impacts of changes in input data.

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