

A mathematical model for maximizing the value of phase 3 drug development portfolios incorporating budget constraints and risk

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We describe a value-driven approach to optimizing pharmaceutical portfolios. Our approach incorporates inputs from research and development and commercial functions by simultaneously addressing internal and external factors. This approach differentiates itself from current practices in that it recognizes the impact of study design parameters, sample size in particular, on the portfolio value. We develop an integer programming (IP) model as the basis for Bayesian decision analysis to optimize phase 3 development portfolios using expected net present value as the criterion. We show how this framework can be used to determine optimal sample sizes and trial schedules to maximize the value of a portfolio under budget constraints. We then illustrate the remarkable flexibility of the IP model to answer a variety of ‘what-if’ questions that reflect situations that arise in practice. We extend the IP model to a stochastic IP model to incorporate uncertainty in the availability of drugs from earlier development phases for phase 3 development in the future. We show how to use stochastic IP to re-optimize the portfolio development strategy over time as new information accumulates and budget changes occur. Copyright © 2013 John Wiley & Sons, Ltd.

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1. Introduction

There is an increasing demand for pharmaceutical products that demonstrate a clear and differentiated value proposition to the patients, prescribers, and payers [1]. There is a need for an approach that explicitly addresses the value proposition during the clinical development process by incorporating research and development, marketing, commercial, and medical affairs perspectives. To this end, we need a tool to compare multiple development options (e.g., doses, designs, endpoints, and budget allocations) with respect to the expected value of the product, which clearly depends not only on the quality of the product itself but also on the quality of the development program.

We develop a quantitative, value-driven approach to the management of pharmaceutical portfolios to maximize their value. We provide an example to demonstrate how our model operates and to show

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its flexibility to address a wide array of options. The example is illustrative of typical decision-making situations in the context of drug development portfolios.

1.1. Assessing the value of a pharmaceutical product

Three key components of assessing the value of a pharmaceutical product are cost, expected revenue, and risk. Numerous factors have an effect on the overall cost, including subject recruitment, investigator and clinician costs, product supply and monitoring costs, costs of data analysis, reporting and interaction with regulatory authorities, and administrative costs. Key factors impacting the expected revenues include indication, affected population size, class/asset share, remaining patent time, external market dynamics, and adherence. Finally, the potential to successfully progress along the drug development path from discovery, through clinical development phases, to regulatory approval, product launch, and commercialization primarily describes risk.

In the development of a drug, there is upfront investment of considerable resources with the expectation of recovering costs and accruing revenues during the later commercialization phase if marketing authorization is granted. The net present value (NPV) is a financial measurement tool that is widely used to evaluate future returns. It represents the difference between the present value of the future returns from an investment and the amount of investment, as described in standard textbooks on financial management [2]. However, as the realization of returns depends on successful development, NPV needs to be extended to apply to situations involving various forms of risk (e.g., a product not being approved). A straightforward extension is the expected value of NPV (ENPV), which represents the NPV weighted by development risks and as such incorporates all three components mentioned at the beginning of this section. We will use ENPV in our model as the criterion for evaluating various development scenarios.

1.2. Assessing the value of a portfolio of pharmaceutical products

A pharmaceutical portfolio will include multiple products and clinical trials. Assessing the value of a portfolio therefore includes all the parameters described earlier and also requires additional considerations. First, budget limits are set not at the product level but at the portfolio level. This makes any decisions interrelated and increases the complexity of decision making. For example, reduction of costs in one program does not only mean immediate savings but also enables increase in investment in other programs.

Further, given the budget constraints, not all planned programs and clinical trials can be executed. One needs to focus on the programs expected to bring the greatest returns, which raises the question of project selection. Burman *et al.* [3] proposed a solution to this problem by a decision tree approach. The resolution to the budget constraints problem, however, should not only be in deciding which projects to select but also on how large they should be. It is standard practice in the industry to fix the sample size of phase 3 studies on the basis of a predetermined level of power (usually 0.80 or 0.90). In this way, a study sample size is not explicitly linked to the commercial value. We argue, on the other hand, that the optimal portfolio development solution should be a combination of project and sample size selections, so that the value of a portfolio as a whole is maximized.

Finally, portfolio optimization cannot be static. Sponsors of phase 3 trials are most often large and medium companies with pipelines of drugs at various stages of development. Phase 3 portfolio development strategy will thus require planning over a time horizon within which a number of viable candidates are expected to become available at various times. Furthermore, many of the potential phase 3 drugs will have uncertainty surrounding their availability because they will be in earlier stages of development and may fail to progress to phase 3. Portfolio planning is also affected by external dynamics. Events, such as approvals of new drugs, would have a major impact on the expected revenues and as such affect the ENPV. Dynamic optimization of the implementation schedules and re-optimization in the light of accumulated information are therefore a key requirement for the phase 3 portfolio optimization.

Having quantified both clinical research and development and commercial components of drug development, we integrate them in a mathematical model that maximizes the value of a pharmaceutical portfolio as a whole. The model uses ENPV as the criterion for phase 3 portfolio optimization. We have focused on phase 3 trials because they are very expensive and, in most organizations, have a separate budget. Our emphasis is on calculating optimal sample sizes for individual studies within a portfolio and subject to budget constraints. The model further simultaneously determines optimal timing of trials, as this also impacts the sample sizes through both budget and patent life considerations. The model can be more broadly applied to a franchise or line of business within a portfolio. Our model incorporates a

risk of drugs in earlier phases of development not passing go/no-go screening prior to entering phase 3. Finally, we show how the model provides a systematic approach to re-optimization over time as new information accumulates and budget changes occur. To our knowledge, this is the first paper to propose a mathematical model that simultaneously optimizes trial designs and trial schedules within budget limits and considers risk from a portfolio perspective.

2. A mathematical model for optimizing clinical research for a portfolio

We develop a mathematical model that optimizes the development strategy for a portfolio of drugs. The model determines optimal sample sizes and schedules of trials for a selection of drugs expected to be available for phase 3 development over the planning period. We show how Bayesian decision analysis can be effectively implemented as an integer programming (IP) model originally developed in the field of operations research. Using IP, one can optimize decisions that are discrete in nature by modeling budgeting constraints, fixed costs, sequencing and scheduling requirements, and many other aspects that arise in the context of optimizing the development of a portfolio of drugs.

2.1. Overview of the model

Previous work on optimization of designs and scheduling of clinical trials at the portfolio level falls into two distinct categories. The first category of papers develops optimization models as a subset of a large amount of work performed in the operations research community and applied to a range of industries [4–12]. Most of the models use IP formulations with budget constraints at their core. Several authors extended the formulation to stochastic programming [4–7]. Others used simulation models [8–12]. Most papers [4–6, 8, 10, 11] use ENPV to measure return with different extensions to include risk, whereas others used real options theory in their modeling [7, 9, 12]. We use ENPV in a decision tree analysis implemented in an IP model, as carried out by Patel and Ankolekar [13]. We decided not to use the real options approach because we agree with [14] that it is difficult to implement it in practice. All these papers, unlike [15], model the probabilities of success at different stages of drug development as fixed, given the values that are inputs to the model. They do not consider the dependency of the probability of having a successful trial on trial design. Our approach differs from theirs in a major way, in that we consider the choice of a design as a key decision variable that influences the probability of success in terms of obtaining regulatory approval and realization of revenues. Although we consider only phase 3 trials in this paper, we have plans to extend our model to include phase 2 trials.

The second category of previous work consists of statistical papers. Although there are several statistical papers that address optimizing design of individual trials using cost–benefit and other economic criteria [16–23], very few view designs from a portfolio perspective. Others, for example, Julious and Swank [24], go beyond the individual trial to discuss application of decision analysis to the clinical development plan of a compound but do not consider the portfolio level. Senn [25] addressed the portfolio problem by ranking candidate drugs using the Pearson index. Zipfel [26] criticized the use of the Pearson index as static and not sensitive to time and therefore will not work well in a common situation where new drug candidates become available while development of older drugs is still in progress. He modeled NPV and cost spending as time-to-event models, with multiple reviews during trials, to consider discontinuation using a modified version of the Pearson index. He modeled available budget as a function of revenues. These papers use indices to optimize portfolio performance. We have chosen to maximize ENPV while meeting budget constraints to incorporate revenue, costs, and uncertainty instead of using a one-dimensional index. We believe that this approach is more intuitive and in line with current practice.

Following Patel and Ankolekar [13], we use a Bayesian prior at the design stage to determine the sample size while assuming that the data resulting from the trial will be analyzed using classical Neyman–Pearson methods. Spiegelhalter *et al.* [27] called this the ‘hybrid classical Bayesian’ approach. It is appropriate for our purpose because a company decides on the sample size for a trial on the basis of all available information, with the objective of deriving economic benefit, whereas the regulatory analysis for approval is typically conducted using classical frequentist theory. Our models have at their core the concept of assurance, convincingly argued by O’Hagan *et al.* [28] as a better basis for selecting sample size than power. Chen and Beckman [16] and Lee and Zelen [29] have used the hybrid approach for sample size determination in clinical trials. Burman *et al.* [30] have described a similar model to

ours for a single clinical trial. The authors in [3] also described this approach as an IP formulation for portfolio optimization that treats the probability of success as fixed as well as illustrates the use of the Pearson index.

The key advantage of our model is that it integrates knowledge from experts in diverse areas of expertise such as clinical research, trial management, clinical operations, statistics, financial analysis, and marketing. The IP formulation is rich in scope and provides the basic framework for quantitative analysis to support a variety of practical decisions arising in the portfolio optimization context.

2.2. Calculation of expected value of net present value

We calculate the ENPV by considering economic factors determined by the choice of sample sizes and scheduling of the clinical trials in the portfolio. We have chosen to incorporate into our models economic factors that are of importance to a company when planning phase 3 clinical trials for new drugs or indications. For example, we assume there is a spending limit specified by a cap on the cumulative expenditure on clinical trial costs for different budgeting periods.

2.2.1. Cash flow model for net present value. Figure 1 shows the cash flow model used for NPV calculations. The cash outflows associated with the conduct of a clinical trial in our model consist of a fixed cost f incurred to set up a trial at the start of the trial at time k and a variable cost component related to n patients enrolled at a rate of λ per month. Assuming a fixed treatment period of b months and a per-patient cost c spread uniformly over that period, the total patient cost amounts to $c\lambda$ per month during a trial period of $n/\lambda + b$ months. At the end of the trial at time $T_a = k + n/\lambda + b$, a fixed setup cost of F is assumed to be incurred, if the trial is successful.

Cash inflows result from sales of the drug when trials are successful. We will consider net cash inflows that result from the difference between the revenue and the variable costs that are incurred to produce and sell the drug. This contribution, R , from sales of a drug will vary over the life cycle of the drug. A typical time profile of contribution would involve three phases including growth, maturity, and decline. In the early growth phase, the contribution would steadily ramp up to a level at which it will remain approximately flat during the maturity phase. As newer, more effective drugs enter the market, or drug patents expire, or similar drugs enter the market, the drug development enters a phase during which contributions steadily decline. We will assume that there is an exclusivity period (T), typically the remaining life of the patent, during which the drug is the sole drug in its target market. We will also assume that at the conclusion of the trial, T_a , a fixed setup time delay, s , is required for regulatory submission work and gearing up for production, distribution, and sales. We assume that the contribution jumps to its peak value at period $T_d = T_a + s$ and remains at that value for a period $t_x = \max[T - T_d, 0]$ until the end of the exclusivity period. Because the bulk of the profits for new drugs comes during the exclusivity period, we will assume that the contribution drops to 0 when it ends. We will not model growth and decay periods or model the effects of competition on revenue. If a model that incorporates these factors is available, we can use it to calculate NPV and use these values in our models instead. Although more elaborate models may be necessary in a specific application, they distract from the illustration of our key ideas.

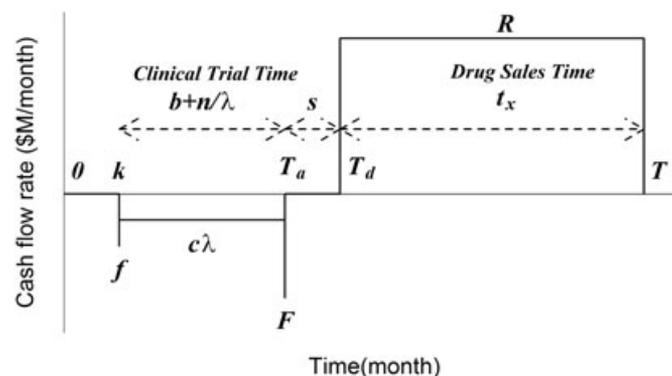


Figure 1. Cash flow model for net present value.

2.2.2. *Trial designs.* Although multiple arms and more complex designs can be incorporated in our model, we focus on trial designs with fixed sample sizes that have two arms: the drug under investigation and placebo. For our example, we assume a balanced design, although imbalanced designs with fixed sample sizes can be readily incorporated into our IP model. We assume a trial setting that requires two identical trials to be conducted for each drug under development.

The key decision variable for our designs is the sample size. For drug i and design j in the portfolio, let us denote the total sample size by n_{ij} for a clinical trial with a balanced design ($n_{ij}/2$ patients on each arm). For a continuous efficacy endpoint following a normal distribution, we have (for example, [31])

$$n_{ij} = 4\sigma_i^2(Z_{\alpha/2} + Z_{\beta_{ij}})^2 / (\delta_i - \delta_i^0)^2, \quad (1)$$

where σ_i is the known common standard deviation of response for drug and matching placebo, δ_i is the mean response to drug therapy, and δ_i^0 is the mean response to the matching placebo. Z_γ is the upper γ quantile of the standard normal distribution with α as the two-sided significance level (typically 0.05) and $(1 - \beta_{ij})$ as power (usually around 0.9). Our formulation requires the user to specify a set of potential sample sizes $\{n_{ij} | j = 1, 2, \dots, J\}$ for each drug $i = 1, 2, \dots, I$ in the portfolio.

2.2.3. *Probability of success.* The IP model can accommodate any model that relates phase 3 sample size to probability of success. The probability can depend on safety as well as efficacy. For simplicity, we will focus on efficacy and assume that there are no safety concerns. We use a hybrid approach that combines Bayesian and frequentist perspectives using the concept of assurance [28]. We specify a prior normal distribution for the continuous endpoint for drug i , with mean δ_i (the same δ_i that is used to compute sample sizes earlier) and standard deviation ψ_i . For the corresponding placebo arm, we assume a normal prior with mean response equal to δ_i^0 and standard deviation equal to ψ_i^0 . Regulatory approval follows if the null hypothesis regarding efficacy is rejected at a two-sided α level of 0.05, independently in each of two separate trials. Both phase 3 trials have the same sample size and are run concurrently.

A standard result from the Bayesian theory [27] is that the predictive probability distribution of mean response is $\hat{y}_i \sim N(\delta_i, \sqrt{(\psi_i^2 + 2\sigma_i^2/n_{ij})})$ for drug i and $\hat{y}_i^0 \sim N(\delta_i^0, \sqrt{(\psi_i^{02} + 2\sigma_i^2/n_{ij})})$ for its placebo. Accordingly, the predictive probability distribution for the difference, $y_i - y_i^0$, is normal with mean $\delta_i - \delta_i^0$ and standard deviation $\sqrt{(\psi_i^2 + \psi_i^{02} + 4\sigma_i^2/n_{ij})}$. The probability of trial success (*PoTS*) for each of two separate trials in the phase 3 program is given by

$$\begin{aligned} PoTS_{ij} &= \Pr(\hat{y}_i - \hat{y}_i^0 > Z_{\alpha/2} 2\sigma_i / \sqrt{n_{ij}}) \\ &= 1 - \Phi \left[\{2Z_{\alpha/2} \sigma_i / \sqrt{n_{ij}} - (\delta_i - \delta_i^0)\} / \sqrt{(\psi_i^2 + \psi_i^{02} + 4\sigma_i^2/n_{ij})} \right]. \end{aligned} \quad (2)$$

Therefore, probability of success (*PoS*) for the phase 3 program as a whole is given by

$$\begin{aligned} PoS_{ij} &= PoTS_{ij}^2 \\ &= \left(1 - \Phi \left[\{2Z_{\alpha/2} \sigma_i / \sqrt{n_{ij}} - (\delta_i - \delta_i^0)\} / \sqrt{(\psi_i^2 + \psi_i^{02} + 4\sigma_i^2/n_{ij})} \right] \right)^2. \end{aligned} \quad (3)$$

2.2.4. *Expected value of net present value.* We designate the time point to which all cash flows are discounted as time 0 and assume that it will take 1 month from that time to start our first trials. (This choice is just to avoid having to add one more symbol to designate this interval.) Let NPV_{ijk} denote the NPV resulting from choosing n_{ij} as the sample size and starting the phase 3 trials in the month k of our development plan, with continuous discounting at a monthly rate ρ . NPV_{ijk} is a random variable that takes one of two values depending on whether the trials result in regulatory approval or not. Let $NPV_{ijk}|G$ and $NPV_{ijk}|NG$ denote the value of the random variable NPV_{ijk} given a regulatory approval outcome of ‘go’ (denoted by G) or ‘no go’ (denoted by NG), respectively.

Extending the notation for cash flows developed earlier by adding subscripts i , j , and k where necessary to reflect dependency on the drug, sample size, and trial starting time, respectively, we have

$$NPV_{ijk}|G = R_i \int_{T_{aijk}}^{T_{dijk} + t_{xijk}} e^{-\rho t} dt - F_i e^{-\rho T_{aijk}} - (2c_i \lambda_i) \int_k^{T_{aijk}} e^{-\rho t} dt - 2f_i e^{-\rho k}, \quad (4)$$

where integrations involving $e^{-\rho t}$ over respective ranges of time refer to continuous discounting at a rate of ρ (for example, [2]) of revenue contribution at a rate of R_i per month and trial cost at a rate of $c\lambda$ per month. The continuous discounting of fixed costs f_i and F_i involves multiplier $e^{-\rho\tau}$, where τ is the time associated with incurring those fixed costs. The last two terms in (4) constitute the present value of the trial cost incurred for both phase 3 trials, irrespective of the approval outcome G and NG. If the trial outcome is NG, there is no revenue, and we have

$$NPV_{ijk}|NG = -(2c_i\lambda_i) \int_k^{T_{aijk}} e^{-\rho t} dt - 2f_i e^{-\rho k}. \quad (5)$$

Combining (4) and (5), we have the ENPV for the phase 3 program as a whole:

$$ENPV_{ijk} = PoS_{ij} \cdot NPV_{ijk}|G + (1 - PoS_{ij}) \cdot NPV_{ijk}|NG. \quad (6)$$

2.3. Integer programming formulation

In this section, we develop the IP model for portfolio optimization.

We will use the following subscripts in our model: i ($i = 1, 2, \dots, I$) for drugs, j ($j = 1, 2, \dots, J$) for designs, k ($k = 1, 2, \dots, K$) for month since the beginning of the planning horizon, and t ($t = 1, 2, \dots, K$) for time in months since start of the two identical phase 3 trials.

The decision variables will be denoted as follows:

$$\begin{aligned} Z_{ijk} &= 1 \text{ if trials for drug } i \text{ with design } j \text{ are started at time } k \\ &= 0 \text{ otherwise.} \end{aligned}$$

Data in our model are defined as follows:

$ENPV_{ijk}$	ENPV of drug i as defined in (6), if $Z_{ijk} = 1$
b_{ijt}	Cumulative total trial cost up to and including month t since the start of trials for drug i with design j
b_{ijTot}	Total trial cost for drug i with design j
B_k	Cumulative budget available up to month k
$kmin_i, kmax_i$	Earliest and latest months for starting trials for drug i
e_{ijk}	Coefficients for formulation of schedule constraints, where

$$\begin{aligned} e_{ijk} &= 1 \text{ if } k < kmin_i \text{ or } k > kmax_i \\ &= 0 \text{ otherwise.} \end{aligned}$$

The objective function to be maximized is the total ENPV for the portfolio calculated using the following formula:

$$\sum_i \sum_j \sum_k ENPV_{ijk} Z_{ijk}. \quad (7)$$

For every drug i , we can make at most one design choice j and can schedule to start it at most in one period k . Accordingly, we formulate the following constraints:

$$\sum_j \sum_k Z_{ijk} \leq 1, \quad i = 1, 2, \dots, I, \quad (8)$$

$$\sum_i \sum_j \sum_k e_{ijk} Z_{ijk} \leq 0. \quad (9)$$

A clinical trial for drug i , with design j , starting at time k , incurs a series of cash outflows including a fixed cost f_i at time k and a monthly variable cost of $c_i\lambda_i$ until time T_{aijk} . Consequently, a decision variable Z_{ijk} will participate in budget constraints related to periods $k, k + 1, \dots$, and so on. For all clinical trials started before time k , Z_{ijk} will also participate in the budget constraint for time k , with a budget

requirement b_{ijt} specific to its duration $t = 1, 2, \dots, k$. We assume that the unused budget from previous periods will be available for use in period k and later, in addition to the new budget injected at time k . We handle this simply by considering the budget requirements b_{ijt} and the budget limit available at time k , B_k , as cumulative values. Accordingly, we formulate the set of K budget availability constraints, wherein the cumulative budget used until and including time k is limited by B_k and all clinical trials Z_{ij1}, \dots, Z_{ijk} that started from period 1 to k , with cumulative requirements b_{ijk}, \dots, b_{ij1} , respectively, determine the cumulative budget used until time k .

$$\sum_i \sum_j \sum_{t=1}^k b_{ijt} Z_{ij(k-t+1)} \leq B_k, k = 1, 2, \dots, K - 1, \tag{10a}$$

$$\sum_i \sum_j \sum_{t=1}^K b_{ij\text{Tot}} Z_{ij(K-t+1)} \leq B_K. \tag{10b}$$

The second equation (10b) of the budget requirement for the final period, K , is different from the first equation, which reflects all the other periods. This is because trials may run beyond the planning horizon provided their budget has been made available by the final period of the planning horizon.

3. Illustrative example

We illustrate our model using an example of a portfolio with seven drugs awaiting phase 3 development. We assume a discount rate of 10% per annum for NPV calculations and an annual budget of \$110m. The planning horizon is 3 years. Trials for each drug can start at the beginning of any month within the horizon. Unspent budget in a year can be carried over to future years in the horizon. Table I shows the financial parameters for the drugs. We assume that the time for regulatory approval and setup for manufacturing, sales, and so on is 6 months for each drug.

Table I. Financial, scheduling, and Bayesian prior parameters and optimum solution.							
	Drug 1	Drug 2	Drug 3	Drug 4	Drug 5	Drug 6	Drug 7
Parameters							
Mean response (δ_i)	0.5	0.4	0.5	0.4	0.4	0.3	0.25
SD of response (σ_i)	2	1.8	2	2	1.5	1.5	1
1st in class?	No	Yes	No	No	Yes	Yes	Yes
SD of Bayesian prior for placebo (ψ_i^0)	0.15	0.15	0.15	0.15	0.15	0.05	0.15
SD of Bayesian prior for drug (ψ_i)	0.15	0.3	0.15	0.15	0.3	0.2	0.3
Trial fixed cost (f_i , K\$)	2805	15	525	2125	240	125	500
Patient cost (c_i , K\$)	11	17	25	24	26	15	14
Fixed setup cost (F_i , m\$)	50	500	400	300	500	300	1000
Contribution (R_i , m\$/month)	175	85	400	200	45	250	500
Market size	M	S	L	M	S	M	L
Exclusivity period (T_i , months)	108	120	135	180	155	180	145
Month when drug will be available for phase 3 trials	1	1	3	6	13	18	25
Enrollment rate (λ_i , patients/month)	30	50	40	60	60	50	45
Treatment period per patient (b_i , months)	0.3	1	12	12	24	6	12
Optimal solution							
Optimal sample size	832	1054	832	1300	732	1300	674
Optimal ENPV (m\$)	4818	1849	10057	5643	457	5959	5754
Optimal schedule (month)	1	1	3	6	13	18	25
Probability of success (Pos_{ij})	0.67	0.49	0.67	0.60	0.49	0.53	0.38

ENPV, expected value of net present value; SD, standard deviation; S, small; M, medium; L, large.

We consider five sample sizes for each drug in the portfolio. These include a sample size of 0 to reflect the option of not including the drug in the optimum development portfolio, as well as four sample sizes corresponding to values of power of 0.8, 0.85, 0.95, and 0.99. Table I gives the parameters for the prior distributions of the mean response for drugs and matching placebos. We assume all priors to be independent normal distributions, and the means of the priors for placebos are equal to 0. Table I also gives the month in which each drug will be available for starting phase 3 trials. We assume that the longest delay in starting phase 3 trials after this earliest time is 3 months for all drugs. Table I gives the optimum sample size for each drug obtained by solving the IP. The optimum time to start each trial is at the earliest possible date. The maximum ENPV for the portfolio is \$34,536m. The second row in the optimal solution section of Table I shows the contribution of each drug to this amount.

A major advantage of an IP formulation is that it can provide answers to a number of important what-if questions. We give some illustrations in the following sections.

3.1. Sensitivity of the expected value of net present value to annual budget

If we reduce the annual budget to \$100m, the IP solution shows that the maximum ENPV for the portfolio reduces from \$34,536m to \$34,528m. Because the reduction in ENPV is 0.02% for a reduction in budget of 9.1%, this might be an attractive alternative to reduce financial exposure. If we reduce the annual budget further to \$90m, the maximum ENPV drops to \$34,388m. A further reduction in the annual budget to \$80m results in an optimum solution that excludes drug 5 from the development program. This suggests that out-licensing of drug 5, available for phase 3 trials in month 13, could be worth considering.

We can vary budget levels over a range and plot the maximum ENPV that can be achieved by a portfolio as a function of the size of its budget. Figure 2 provides an example of such a plot. The plot illustrates how reducing the budget to about \$50m has a small effect on the maximum ENPV, but a further reduction results in a sharp drop thereafter. If funds can be borrowed at differing interest costs depending on their amounts, such a plot can help in making decisions regarding the amount to borrow.

3.2. Out-licensing a drug

If we are considering out-licensing a drug, say, drug 5, we can rerun the IP model after removing drug 5 from our portfolio. A few additional runs of the IP model using different budgets result in an optimum solution for ENPV of \$34,079m with an annual budget of \$85m. The best ENPV that includes drug 5 for an annual budget of \$85m would be \$34,158m, with a contribution of \$419m from drug 5. This implies that we will be better off if we can out-license drug 5 for a net licensing fee that exceeds \$79m. For example, an out-licensing fee of \$100m would yield an optimal ENPV of \$34,179m, which is higher than \$34,158m with drug 5 in the portfolio and with its own contribution of \$419m. We can explain this seemingly counterintuitive outcome in terms of the positive impact of out-licensing beyond the licensing fee it acquires, as it effectively releases the budget for better decisions on the remaining drugs. We can easily incorporate the out-licensing decision in the IP model, by adding a design alternative, say $j = 0$, with $ENPV_{i00}$ equal to the licensing fee and b_{i00} equal to the cost, if any, of implementing the out-licensing decision.

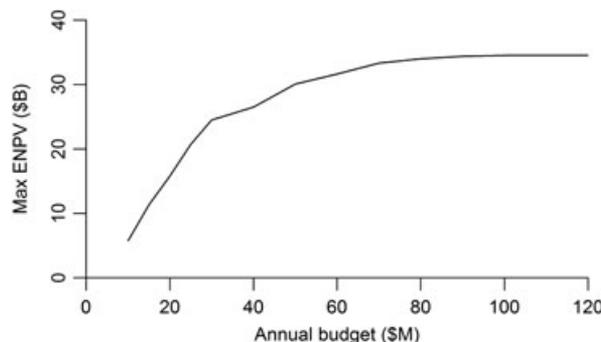


Figure 2. Sensitivity of the expected value of net present value (ENPV) to annual budget.

3.3. In-licensing a drug

Now, consider in-licensing a drug from another company. If we develop an ENPV model for the drug as we have performed for company drugs and select a set of candidate sample sizes for the in-licensed drug, we can add it as drug 8 to the IP model. Let us suppose that the data on drug 8 are $\lambda_8 = 50$ per month, $b_8 = 27$ months, $c_8 = \$23\text{K}$ per patient, $f_8 = \$1390\text{K}$, $F_8 = \$100\text{m}$, $R_8 = \$300\text{m}$ per month, $T_8 = 165$ per month, $\delta_8 = 0.5$, $\delta_8^0 = 0$, $\psi_8 = 0.5$, and $\psi_8^0 = 0.3$. Let us assume a scenario where drug 8 will be ready for phase 3 trials between 13 and 16 months from now, we have out-licensed drug 5, and we wish to consider an annual budget of \$100m. This gives us an opportunity to consider adding drug 8 to our portfolio. This addition will yield an optimal ENPV for the portfolio of \$37,651m, an increase of \$3123m over the case when we had drug 5 instead of drug 8 in the portfolio. The model achieved this increase through the additional contribution of \$3572m from drug 8 with a sample size powered at 0.95 and a start of phase 3 trial in month 13.

4. Stochastic integer programming formulation

A limitation of the IP formulation in the previous section is that it considers the availability of drugs for phase 3 trials to be certain. In this section, we extend the formulation to a stochastic IP (SIP) model [32] to address uncertainty in the availability of drugs due to possible uncertain outcomes during earlier phases of drug development. In view of the inherent complexity of such models, we have simplified the finer scheduling decision within an interval compared with the IP formulation, by assuming that the drug i trial will be scheduled at the time of its potential availability, $k_i = k_{\min_i} = k_{\max_i}$, with $k_1 \leq k_2 \leq k_3 \dots \leq k_I$. Consequently, the subscript k will be dropped from the decision variable Z_{ijk} and data coefficient $ENPV_{ijk}$.

We address the uncertainty in availability of a drug for phase 3 trials in the SIP formulation through Bernoulli random variables defined as follows:

$$\begin{aligned} a_i &= 1 \text{ if drug } i \text{ is available (clears go/no-go hurdle for phase 3 development)} \\ &= 0 \text{ if drug } i \text{ is not available (fails to clear go/no-go hurdle),} \\ p_i &= \text{Probability } (a_i = 1) \text{ independent of } a_j \text{ for } j \neq i. \end{aligned}$$

A sequence of realizations of random variables $a_1, a_2, a_3, \dots, a_{i-1}$ corresponding to its preceding drugs define a potential availability history of drug i . We assume that drug 1 is available with certainty in period 1 (i.e., $a_1 = 1$, $p_1 = 1$, and $k_1 = 1$). Consequently, we will drop the explicit use of the terms a_1 , p_1 , and k_1 from further definitions. This also implies that drug 1 has no predecessor and drug 2 has an implicit history of drug 1 being certainly available.

The decisions for a drug are contingent on the availability history of its predecessor drugs. Accordingly, the decision variables will be denoted as

$$\begin{aligned} Z_{ij} &= 1 \text{ if drug } i \text{ trial uses design } j \\ &= 0 \text{ otherwise, for } i = 1, 2 \text{ and } j = 1, 2, \dots, J, \\ Z_{ij|a_2a_3\dots a_{i-1}} &= 1 \text{ if drug } i \text{ trial uses design } j \text{ given availability history } a_2a_3\dots a_{i-1} \\ &= 0 \text{ otherwise, for } i = 3, 4, \dots, I \text{ and } j = 1, 2, \dots, J. \end{aligned}$$

Each decision variable $Z_{ij|a_2a_3\dots a_{i-1}}$ has a probability of $p_i \prod_{m=2}^{i-1} p_m^{a_m} (1 - p_m)^{1-a_m}$ associated with its availability history. This probability is used to weight the corresponding objective function value term $ENPV_{ij} Z_{ij|a_2a_3\dots a_{i-1}}$. Accordingly, the objective function to be maximized is given by

$$\begin{aligned} &\sum_j ENPV_{1j} Z_{1j} + p_2 \sum_j ENPV_{2j} Z_{2j} \\ &+ \sum_{i=3}^I \sum_{a_2} \sum_{a_3} \dots \sum_{a_{i-1}} p_i \prod_{m=2}^{i-1} p_m^{a_m} (1 - p_m)^{1-a_m} \sum_j ENPV_{ij} Z_{ij|a_2a_3\dots a_{i-1}}. \end{aligned} \tag{11}$$

Unlike its IP counterpart in (7) that specifies ‘do this’ as an optimal decision for each drug, maximizing the objective function (11) yields an *optimal policy* specifying ‘do this, if ...’ as a set of optimal decisions for each drug, contingent on its availability history.

Design constraints are defined as in (8) to ensure that only one of the designs can be selected for a drug with a given history of availability.

$$\sum_j Z_{ij} \leq 1, \quad i = 1, 2, \quad (12a)$$

$$\sum_j Z_{ij|a_2 a_3 \dots a_{i-1}} \leq 1, \quad i = 3, 4, \dots, I, \quad a_m = 0, 1, \quad m = 2, 3, \dots, i - 1. \quad (12b)$$

Budget constraints for each of the periods in the planning horizon are defined as in (10), but we need to define them in the context of each instance of availability history to ensure the feasibility of an optimal decision policy.

At the starting periods until the potential availability of drug 2 at k_2 , drug 1 is the only contender for the available budget. So,

$$\sum_j b_{1jk} z_{1j} \leq B_k \text{ for } k = 1, 2, \dots, k_2 - 1. \quad (13a)$$

Until the potential availability of drug 3 at k_3 , drugs 1 and 2 are the joint contenders for the available budget from k_2 onwards,

$$\sum_j b_{1jk} z_{1j} + \sum_j b_{2j(k-k_2+1)} z_{2j} \leq B_k \text{ for } k = k_2, \dots, k_3 - 1. \quad (13b)$$

For the budget period k_3 onwards, the set of contenders for the available budget is contingent on the availability history of predecessor drugs with related random variables coming into play. So,

$$\begin{aligned} \sum_j b_{1jk} z_{1j} + a_2 \sum_j b_{2j(k-k_2+1)} z_{2j} + \sum_j b_{3j(k-k_3+1)} z_{3j|a_2} \leq B_k \\ \text{for } a_2 = 0, 1 \text{ and } k = k_3 \dots k_4 - 1, \end{aligned} \quad (13c)$$

and so on.

For periods after the potential availability of the last drug I , all the 2^{I-1} possible subsets of predecessor drugs would be the contenders, contingent upon related availability histories. So,

$$\begin{aligned} \sum_j b_{1jk} z_{1j} + a_2 \sum_j b_{2j(k-k_2+1)} z_{2j} + a_3 \sum_j b_{3j(k-k_3+1)} z_{3j|a_2} + \dots \\ + a_{(I-1)} \sum_j b_{(I-1)j(k-k_{I-1}+1)} z_{(I-1)j|a_2 a_3 \dots a_{(I-2)}} + \sum_j b_{Ij(k-k_I+1)} z_{Ij|a_2 a_3 \dots a_{(I-1)}} \leq B_k \\ \text{for } a_2, \dots, a_{I-1} = 0, 1 \text{ and } k = k_I \dots K - 1. \end{aligned} \quad (13d)$$

Finally, for the last period, K , we ensure that the total budget requirement, $b_{ij\text{Tot}}$, for each of the drugs will be met, as in (10b).

$$\begin{aligned} \sum_j b_{1j\text{Tot}} z_{1j} + a_2 \sum_j b_{2j\text{Tot}} z_{2j} + a_3 \sum_j b_{3j\text{Tot}} z_{3j|a_2} + \dots + \\ a_{(I-1)} \sum_j b_{(I-1)j\text{Tot}} z_{(I-1)j|a_2 a_3 \dots a_{(I-2)}} + \sum_j b_{Ij\text{Tot}} z_{Ij|a_2 a_3 \dots a_{(I-1)}} \leq B_K \\ \text{for } a_2, \dots, a_{I-1} = 0, 1. \end{aligned} \quad (13e)$$

4.1. Example (continued)

Suppose that drugs 1 and 2 are available for phase 3 trials, but the probabilities of drugs 3 through 7 entering phase 3 development are 0.1 for all the drugs (estimated from past development experience and published information), except drug 6 in which we are very confident and for which the probability of entering phase 3 is 0.9. Considering the low probability (about 0.0001) of having to fund development of all drugs, let us consider a lower total available budget of \$128m for the planning horizon of 3 years. Uncertainty in availability of drugs for phase 3 development impacts the maximum ENPV very substantially. The maximum ENPV drops from \$34,536m to \$13,889m.

The optimal solution is given in column 3 of Table II. Note that the optimum sample size varies with the history of availability of earlier drugs. For example, for drug 6, the optimal sample size is 1300 if

Table II. Optimal solutions for stochastic integer programming model examples.

Drug	Decision variables = 1	Optimal sample size		
		Month 1	Month 4	Month 7
1	Z14	832	832	832
2	Z22	728	728	728
3	Z341	832	—	—
4	Z4210	898	898	898
5	Z511100	442	442	—
6	Z641000	1300	1300	—
6	Z641001	1300	1300	—
6	Z641010	—	—	1300
6	Z641011	—	—	1300
6	Z621010	898	898	—
6	Z621011	898	898	—
6	Z621100	898	—	—
6	Z621101	898	—	—
6	Z621110	898	—	—
6	Z621111	898	—	—
7	Z7210000	576	576	—
7	Z7210001	576	576	—
7	Z7210010	576	576	—
7	Z7210011	576	576	—
7	Z7210100	576	576	576
7	Z7210110	576	576	576
7	Z7211000	576	—	—
7	Z7211010	576	—	—
7	Z7211100	576	—	—
7	Z7211110	576	—	—
7	Z7110101	—	—	504
7	Z7110111	—	—	504

drugs 3 and 4 are unavailable and is 898 if either or both are available. Although it is optimal to develop drug 6, it is worthwhile to develop drug 4 only if drug 3 is not available and drug 5 only if both drugs 3 and 4 are unavailable. We have, in fact, an optimal policy giving us the sample size we would choose for every possible future availability scenario for drugs in the future.

Now, suppose we are at month 4 and drug 3 has failed to qualify for phase 3 trials. We can rerun the SIP model with this new information. (Actually, we do not need to do this; we can simply set all the decision variables in the optimal solution at month 1 with $a_3 = 1$ to 0 to obtain the optimal solution for month 4 because the only additional information we have is that drug 3 is not available.) The new maximum ENPV is \$13,010m (discounted to month 1 to enable comparisons), a reduction of \$879m from our expected maximum ENPV of \$13,889m at month 1. Column 4 of Table II shows the optimum solution at month 4.

Now, suppose we are at month 7 having started trials for drug 4 in month 6 because drug 4 did make the cut for launching phase 3 trials. Furthermore, we learn that the drug 6 development program is delayed so that its anticipated availability is month 23 instead of month 18. We also learn that drug 6 is not as likely as we expected to reach phase 3, so we decrease p_6 from 0.9 to 0.6. Drug 7, on the other hand, looks much more promising than it did earlier, so we increase p_7 from 0.1 to 0.5. Let us suppose that, because of having drug 4 in phase 3, management decides that the budget can be increased by \$22m. Column 5 of Table II gives the revised optimal solution in light of this information.

The maximum ENPV is \$17,911m, which is higher than what we had expected earlier. The availability of drug 4 for phase 3 trials and the increased probability of entering phase 3 for drug 7 have caused this increase that offsets the reduced outlook for drug 6, along with the possibility of phase 3 development of drug 7, even if drugs 5 and 6 become available because of the increased budget.

The optimal policy involves a trial expense of \$149m if all drugs become available. Note that drug 5 is not developed even if it were to be available because of its low ENPV contribution in comparison with

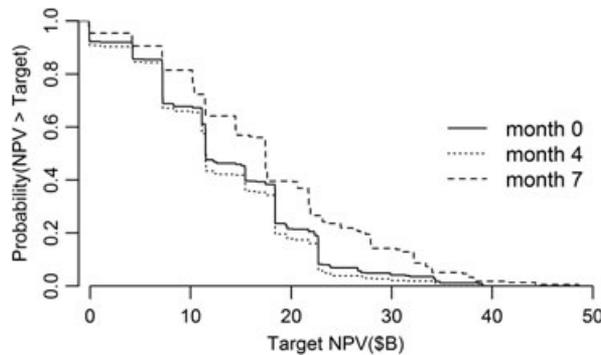


Figure 3. Complementary cumulative distribution of net present value (NPV).

drugs 6 and 7, which could become available later. Drug 5 is a good candidate for partnering. Suppose we are able to find a partner with more experience in the therapeutic area of drug 5. We estimate that this is likely to increase the probability of availability for drug 5 to 0.5 within the same pre-phase 3 development schedule. After negotiations, we are considering a contract in which we share equally in costs and net revenue if phase 3 trials are successful. Our share of cost and ENPV would be \$10m and \$200m, respectively. The partnering option for drug 5 is incorporated as a ‘pseudo-design’, with appropriate probability of availability, budget, and ENPV coefficients in the SIP model. The maximum ENPV with this partnering option increases to \$17,940m within the budget of \$150m. The optimum solution is to exercise the partnering option, increase the sample size for drug 7 from 504 to 576 if both drugs 5 and 6 become available, and reduce the sample size for drug 6 from 1300 to 898 to stay within the budget.

Note that we could consider partnering options for as many drugs as we like and indeed competing contracts and partners for each drug using the device of ‘pseudo-designs’. For example, let us consider the situation at month 1 in our example with the option of partnering for all drugs. Suppose that the partnering arrangement for any drug is that we receive 50% of the profit and the trial costs are funded by the partner. In this case, the maximum ENPV is \$13,971m, which is higher by \$82m than the maximum ENPV without partnering of \$13,889m. The optimum solution chooses the partnering option for drug 5. For drug 4, the partnering option is chosen only if drug 3 becomes available. Drug 7 is chosen for partnering only when drugs 3 and 6 are both available or when drug 3 is unavailable and both drugs 4 and 6 are available.

4.2. Risk associated with the expected value of net present value maximizing portfolio

In this paper, we have used ENPV as the criterion for optimizing the return on our portfolio. Although this is commonly used in practice, it does not account for the downside risk from low and negative returns. The distribution of NPV gives us insight into the risk of a portfolio. We have estimated the complementary cumulative distribution of the NPV of the optimum solutions at months 1, 4, and 7 as given in Table II. We used 10,000 Monte Carlo samples of the success probabilities and availability histories to produce the results shown in Figure 3.

It is interesting to note that the probability of making a loss on the portfolio is 0.09 for months 1, 4, and 7. The probabilities of the portfolio NPV exceeding \$10bn are 0.67, 0.66, and 0.72 at months 1, 4, and 7, respectively. The chances of exceeding \$20bn increase from 0.23 in month 1 to 0.31 in month 7. Prospects of exceeding \$30bn increase by nearly double from months 1 to 7, from a probability of 0.07 to 0.13.

5. Discussion

We have developed a mathematical model that maximizes the value of a portfolio by determining the optimal sample sizes of phase 3 trials under budget constraints. We constructed an IP model that provides the basic framework for portfolio optimization, using ENPV as the criterion. Our approach provides a more realistic solution to portfolio optimization than models without budget limits. For most indications, the cost of phase 3 trials is a tiny fraction of potential revenues. Therefore, the PoS and factors impacting

the revenues would override the impact of cost in such models. In the absence of a budget constraint, if there is even a small probability of a marketing approval, it will lead to a positive ENPV. The optimal solution for a typical portfolio would then be to optimize each trial separately.

However, when there is a budget limit, optimizing each drug separately and prioritizing to satisfy the budget limit is not a good alternative compared with optimizing the IP model with budget constraints. Consider, for simplicity, a portfolio with just drugs 1 to 4 in Table I and a total 3-year budget of \$120m. If we optimize each drug's sample size separately, we will need a budget of \$168m. If we prioritize the drugs according to their ENPV to satisfy the budget limit, we would choose drugs 3 and 4, giving an ENPV of \$15,700m. If we prioritize using the ratio of ENPV to trial cost for each drug (the 'bang-for-the-buck' principle), we choose drugs 1, 2, and 3 to obtain an ENPV of \$16,724m. Using the IP model and constraining the budget to \$120m, we obtain an optimal ENPV of \$22,367m.

Drug development is a process with a very high level of uncertainty. Numerous internal and external factors can impact outcomes of interest and may require major shifts in development strategies. This problem can be alleviated by incorporation of stochastic elements in the model. We extended the IP framework to an SIP model that incorporates uncertainty of availability of drugs for phase 3 trials in the future. SIP provides an optimal policy that specifies the optimal sample size for each drug for every possible scenario of availability of future drugs for phase 3 trials. There is also a great uncertainty in other internal factors, as well as in external factors, such as approvals of competing products. Stochastic elements that reflect these uncertainties could also be built into our models. The objective of our paper and our example, however, is not to address all possible sources of uncertainty but rather to develop and describe a framework within which this could be carried out.

We should also consider re-optimization to dynamically manage uncertainty. Optimization can only provide the best solution and strategy for the portfolio development on the basis of the information known at the time when the portfolio is analyzed. The right time to consider re-optimization is after any new information, either internal or external, has been received. We have shown how our models enable dynamic re-optimization of the portfolio as new information becomes available and changes in budget occur.

A limitation of our IP and SIP models is that they are based on ENPV. Although ENPV is a commonly used criterion in large pharmaceutical companies, it implies indifference to the downside risk. We are working on extending the model to optimize expected utility to reflect risk-averse decision making [33]. We are also exploring models that maximize the probability of meeting specified revenue or NPV targets. Such models are likely to be more appropriate for smaller portfolios and companies that depend on venture capital.

In practice, it is not unusual for phase 2 studies to result in go decisions to phase 3 even though the drug is ineffective for the phase 3 clinical endpoint. This may happen for a number of reasons. Three examples are as follows: an unreliable biomarker or surrogate endpoint was used in phase 2, the dose selected for phase 3 was inappropriate, or the phase 2 and 3 populations differ in their response to the drug. We incorporate this idea in our model by allowing the prior for some drugs to have a probability point mass at δ_i^0 . In our SIP example, if we modify the priors for drugs 1 through 4 to each have an 80% probability of being ineffective, the maximum ENPV at month 1 drops drastically from \$13,889m to \$7455m for a budget of \$128m. The optimum sample sizes for drugs 2, 3, and 4 are reduced to 636, 504, and 786 subjects, respectively. The optimal sample size for drug 5 is increased to 506. For drug 6, the optimal sample size depends on the availability of drugs 2 to 5. If drugs 2 and 4 become available, the optimal sample size decreases to 786; if none of these drugs or just drug 5 becomes available, the optimal sample size is unchanged; in all other drug availability situations, the optimal sample size is increased to 1300.

Given its flexibility, our framework can be used to handle several important aspects of portfolio optimization. We give some examples in the following.

- (1) We can perform valuable sensitivity analysis easily by running a series of IP or SIP models. Similarly, we can use modifications of parameters in our models to perform what-if computations relating to sharing of costs and revenues for phase 3 development of drugs in a partnership or joint venture. We have described such what-if computations for out-licensing and in-licensing decisions in Sections 3.2 and 3.3 and for partnering in Section 4.1. Another example would be varying the trial times in a series of IP or SIP runs for a drug with highly uncertain or nonconstant enrollment rates by using appropriate values of b_{ijk} . One more example would be to assess the impact of market uncertainty for a drug by varying the value of the net revenue parameter, R_i .

- (2) We have modeled R_i as dependent solely on the regulatory approval. If we believe that R_i will also depend on the magnitude of the effect size, D_i , we can incorporate this into our framework by replacing R_i with $R_i(D_i)$. Accordingly, R_i will be replaced by the expectation of $R_i(D_i)$ in the first term of (4), where the expectation is taken over the conditional posterior distribution of $D_i|G$ computed by updating the prior of D_i . Using this value of $NPV_{ijk}|G$ in (6) will reflect the influence of effect size on $ENPV_{ijk}$.
- (3) We can incorporate the impact of safety concerns and adverse side effects on PoS and revenue by using a bivariate model for safety and efficacy with an appropriate prior (for example, [34]). The expressions (2)–(5) will then involve bivariate integrals that may need numerical integration. The results are combined using (6) to calculate $ENPV_{ijk}$. However, these calculations will need to be performed only once outside of the IP and SIP computations.
- (4) We can reflect the impact of competition if we can model when a competing drug is likely to come to market and the extent to which it would reduce market share for a drug in our development plan. We would modify $NPV_{ijk}|G$ for the affected drug using this model.
- (5) If we wish to treat recruitment for trials as a random process, we can find the optimal policy using expected values of recruitment times in the IP and SIP formulations. Using Monte Carlo simulation to generate samples of recruitment times, we can estimate the sensitivity of NPV for this policy to the randomness in recruitment. However, the optimal policy computed earlier will not optimize for uncertainty in recruitment in determining the policy. If the recruitment rate can be estimated before the trial to be fast, moderate, or slow but not at the time of calculating the optimal policy, we can use a discrete distribution with a few support points (say, fast, moderate, and slow) and formulate the problem of randomness in recruitment times as an SIP.
- (6) A limitation of our model is that we assume that drugs that we develop have independent parameters for priors and probability of availability. We can model dependency between two drugs in net revenue using estimates for the case when both drugs are taken to market. Other dependencies such as those in effect size and availability would require correlated parameters.
- (7) We are currently working on portfolio planning for trials with adaptive or group sequential designs in phase 3. The formulation we have used for SIP may not be computationally adequate for this and other larger problems. We are exploring SIP formulations that use ‘independent scenario formulations’ coupled with ‘nonanticipatory’ constraints because there are powerful algorithms available for computing or approximating optimal solutions for SIPs with this formulation [32].

In conclusion, the portfolio optimization problem for new drug development is complex and involves integration of knowledge of experts with diverse specializations. We see our paper as a first step that provides an attractive quantitative framework using IP and SIP models to structure the dynamic and unpredictable elements of the problem.

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