

# Combining drug–disease and economic modelling to inform drug development decisions

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Drug–disease models and clinical trial simulations are increasingly being used to support trial design and treatment optimization decisions. Less widely recognized is their potential for guiding strategic development decisions. These decisions require economic valuation of the potential product profile of efficacy, safety, ease of use, and so on. This review presents a disguised case study that uses drug–disease modelling to generate a probabilistic forecast of a drug's profile. This allows a quantitative analysis of whether to pursue a once-a-day regimen for an antiretroviral being tested twice-a-day in Phase II trials, and if so, at what dose and for which market segments.

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▼ Models of disease progression in the presence of therapeutic drugs are especially useful when embedded in Monte Carlo simulations of clinical trials<sup>1</sup>. These simulations use random draws to represent the variability of relevant characteristics across the sub-population included in the trial. By adjusting trial design parameters, such as the number of patients and dose levels in each arm of a trial, it is possible to identify more informative and efficient trial designs.

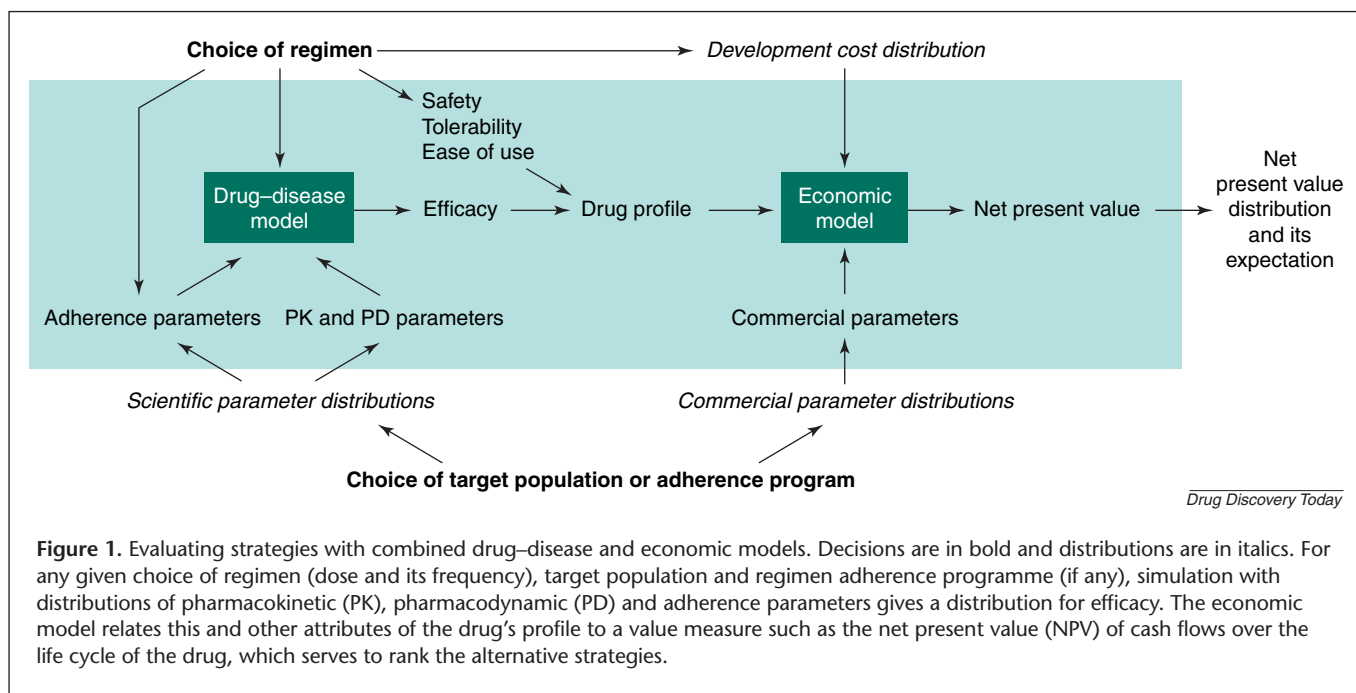
But what about strategic questions, such as which patient population to target, and whether to develop a more convenient dosing regime? Drug–disease modelling and simulation are again useful for such decisions, when coupled with economic modelling that captures the range of possible values of the drug's profile in the market (Fig. 1). The approach taken here is decision analysis, which rigorously integrates decisions, uncertainties, and value measures. This approach has been applied to drug R&D strategy from discovery to post-launch planning<sup>2</sup>, but its usefulness

in combination with scientific modelling and simulation is under-appreciated.

The case study below, disguised but based on a consulting project with a clinical development team, illustrates the use of coupled drug–disease and economic models to guide decisions about developing a once-a-day regimen for a drug in late-stage development and to identify implications for discovery prioritization. These decisions required answers to both scientific and economic questions – for example, would the once-a-day regimen provide adequate protection with commonly observed lapses in dose-taking behaviour (adherence or compliance to the regimen), and would the increased market share from switching from twice-a-day to once-a-day dosing pay for higher development costs?

## The case

An HIV protease inhibitor was completing dose-finding trials with twice-a-day dosing. However, competing drugs with the convenience of once-a-day dosing were in clinical trials. Based on encouraging pharmacokinetic (PK) studies and efficacy results, the clinical development team believed that once-a-day dosing of its drug could be successful, at least in 'naive' patients who have not yet started antiretroviral therapy and thus are unlikely to have resistant virus. By contrast, 'experienced' patients tend to develop resistance more quickly, especially if their adherence is imperfect. For example, in a study of 81 mostly experienced HIV patients, Paterson *et al.* showed dramatically higher rates of viral failure (defined as >400 viral copies ml<sup>-1</sup>) among patients with lower adherence (defined as the



percentage of prescribed doses actually taken)<sup>3</sup>. Failure rates increased from 22% of patients with adherence above 95%, to 82% of patients with adherence below 70%.

These results were for drugs taken two or three times daily; the consequences of missing the same fractions of once-a-day drugs may be worse because of the longer inter-dose intervals<sup>4</sup>. As a result, the clinical development team believed that a once-a-day regimen would have too high a failure rate in experienced patients, unless perhaps it incorporated an adherence monitoring and improvement programme. This would add substantial cost: for example, a programme using pill vials fitted with an electronic opening monitor and alarm, a modem for transmitting the opening times, and nurse monitoring and follow-up services would cost ~US\$1000 per year. However, such programmes have been shown to be effective in hypertension, and even the monitoring alone improves adherence for some patients<sup>5</sup>. Although a formal cost-benefit analysis would be desirable to evaluate whether the benefits of such a programme outweigh the costs, a simpler strategic analysis would be worthwhile, in the context of experienced patients with once-a-day dosing.

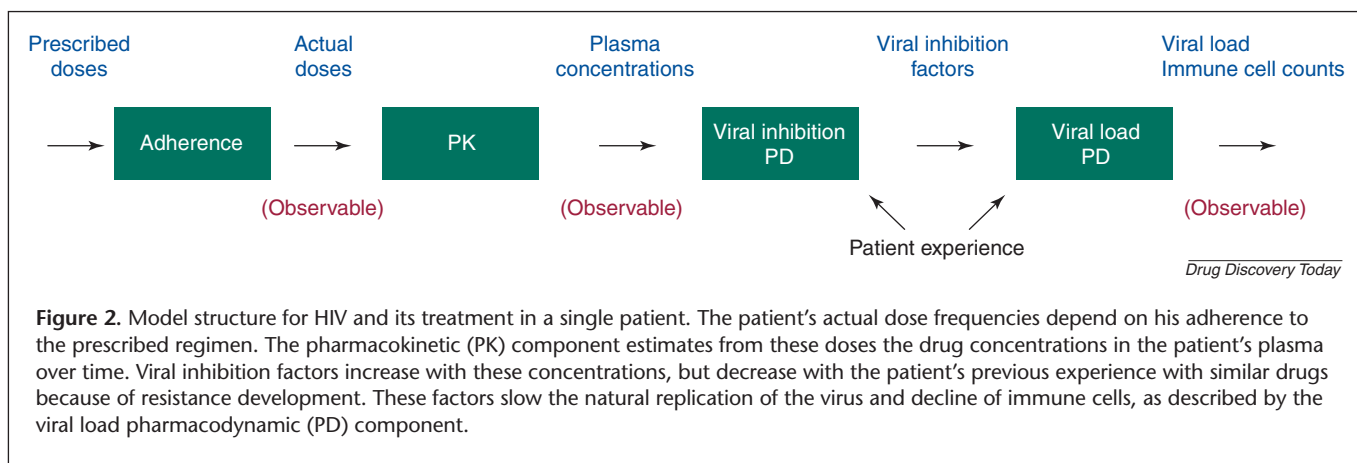
The simplest once-a-day regimen to develop would use the total daily dose of the twice-daily drug as a single dose. However, this dosage might worsen the usual side effects, such as nausea, enough to cause patients to adhere poorly or switch regimens. Therefore the team considered an alternate formulation with less than double the twice-a-day dose and with slower absorption. Developing this formulation would delay remaining trials by several

months, and it could fail or show lower efficacy. The development team decided that the following four strategies were worthy of quantitative analysis:

- Continue with the twice-a-day formulation only, for both naive and experienced patients;
- Administer doubled doses once-a-day to naive patients and the twice-a-day formulation to experienced patients;
- Administer doubled doses once-a-day to experienced patients participating in an adherence programme, as well as to naive patients;
- Develop the new once-a-day formulation, targeting experienced as well as naive patients.

### Drug-disease model

Analyzing these strategies required a model to predict the success of the various regimens. Figure 2 shows the four components of the drug-disease model that the team developed. The regimens considered were typical of Highly Active Antiretroviral Therapy (HAART), combining two reverse-transcriptase inhibitors (RTIs) with the protease inhibitor (PI) under investigation for all patients, as well as a second PI for experienced patients. The adherence model component expressed the variability in a patient's dosing schedule relative to the prescribed schedule for each drug. Three levels of variability were considered: in the fraction of prescribed doses that are actually taken over a long period, in the clustering of missed doses into 'drug holidays', and in the timing of doses taken around the prescribed 12-hour or 24-hour intervals. Distributions for



these types of variability were based on electronic records from studies with pill bottle caps that record opening times, as well as adherence literature (see Ref. 6 and AARDEX's Electronic Monitoring Bibliography at <http://www.aardex.ch/bibliography.htm>).

Second, the PK model component consists of a system of differential equations relating doses to drug concentrations in plasma over time, accounting for drug accumulation from dose to dose, as well as gradual changes induced by the drugs in the activity of enzymes that metabolize the drugs. The equations have parameters for bioavailability, absorption and clearance rates, enzyme activity over time, and so on. Most of the parameters are unobservable and, therefore, were estimated from clinical trial data with a nonlinear regression package, such as NONMEM (NONLinear Mixed Effects Model; see <http://c225.ucsf.edu>). This provides not just point estimates of parameter means, but also variances and covariances, reflecting variability across patients and uncertainty in the parameter estimates.

Third, the viral inhibition pharmacodynamic (PD) component uses parametric models known as sigmoid Emax functions to relate the plasma concentrations of the drugs to fractional viral-inhibition factors. PIs reduce viral replication rates, so a PI inhibition factor multiplies the modelled viral replication rates. Similarly, RTIs reduce infectivity, so an RTI inhibition factor multiplies the modelled cell infection rates.

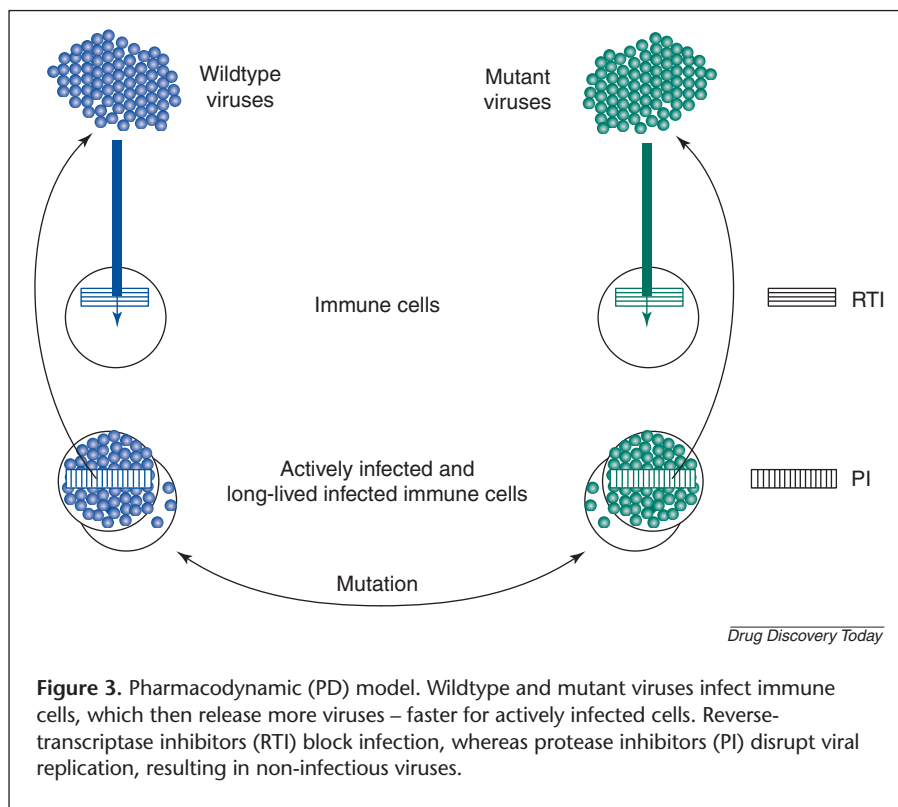
Increasingly sophisticated viral load PD models have been developed for HIV over the past decade, but the essence is the same: a predator-prey relationship between HIV and the immune cells it infects<sup>7</sup>. As therapy allows the immune cell population to start recovering, the virus finds more prey, which can lead to viral rebound and subsequent oscillations in virus and immune cell levels. The relationships are described by a set of differential equations for the levels of each of various types of HIV and immune cells

over time. For example, our model assumed that the growth rate of each type of virus increases linearly with the number of each type of immune cell, and decreases linearly with the current viral load because of natural viral deaths.

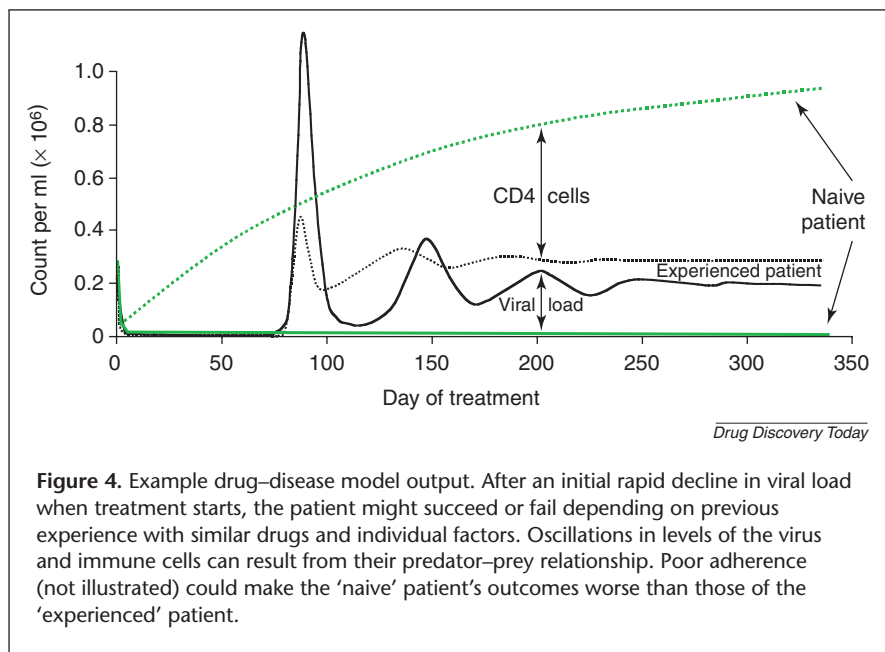
The PD equations have parameters for rates of infection, viral production, viral removal, and so on, which are estimated as for the PK model, based on trial observations of total viral load and immune cell counts. Figure 3 illustrates the model, which used two virus types (wildtype and mutant) and three cell types (uninfected, actively infected, and latently infected). More complex models recognize more types of each, but this was sufficient to capture the key characteristics of infection and response to drugs for the purpose of this analysis.

Mutant virus differs from wildtype virus in that it has developed one or more mutations that make it much less susceptible to particular drugs. Resistance to a drug develops quickly when the drug is present in low concentrations, selecting for the mutations and allowing rapid viral replication. This happens when adherence to the regimen falters, or when the patient's clearance or bioavailability parameters make drug concentrations sub-optimal. When resistance develops, the patient switches to drugs with dissimilar resistance profiles, but after repeated failures choices become limited because of overlapping patterns of resistance among the nine RTIs and six PIs approved by the end of 2000.

Each component of the drug-disease model has limited value by itself, but together the components can predict short-term and long-term efficacy as a function of controllable variables, such as the regimen, and partially controllable variables such as adherence. The primary output of the drug-disease model is the expected fraction of patients who 'succeed', or who have viral loads below a threshold, such as 400 copies ml<sup>-1</sup>, after one year of the new treatment. (Although the latest tests can detect fewer than 10 copies ml<sup>-1</sup>,



a threshold of 400 copies has the advantage of ignoring unimportant random fluctuations in viral load around lower levels.) The drug–disease model calculates an individual patient’s outcome by integrating the differential equations over the year, given a simulated schedule of doses and PK and PD parameters. Figure 4 shows an example of the model results. Monte Carlo simulation of many



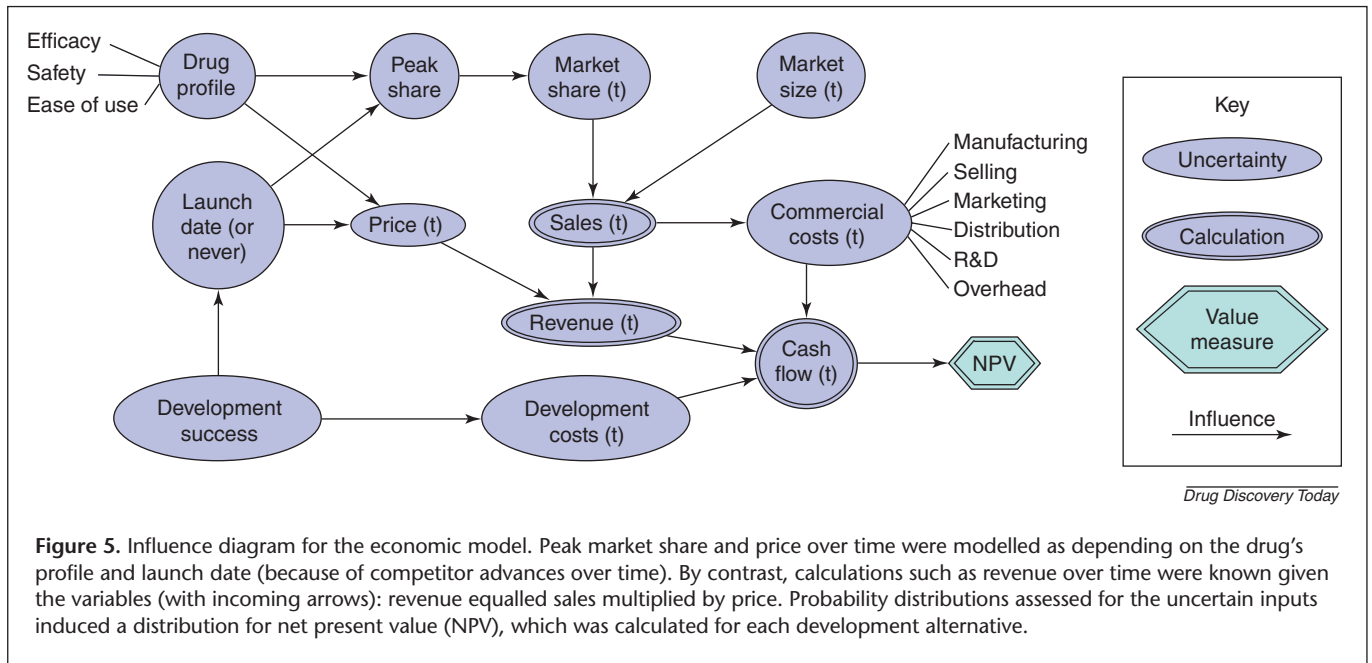
patients, with parameters drawn from the population being studied, gives the overall success rate. Simulation could also provide a distribution of possible results of any specific trial, accounting for trial size, dropout rates, and so on.

### Economic model

The economic model translated a drug profile – a set of attributes in categories such as efficacy, safety, tolerability and usability – into a value measure for decision-making. The team chose as its value measure the net present value (NPV) of after-tax cash flow over the life cycle of the drug. Of course, this was highly uncertain, but once the uncertainty was carefully quantified, the expected or probability-weighted average NPV was calculated and used to compare alternatives, together with plausible ranges around the expected values.

Simple sets of parameters were used to express all model inputs, facilitating probabilistic analysis, as described below. To relate the profile to NPV, the team first related it to peak market share and price, as illustrated in the influence diagram (a network description of probabilistic relationships<sup>8</sup>) of Fig. 5. Peak share was translated to share-over-time with the simple shape shown in Fig. 6. Share multiplied by market size gave sales; sales multiplied by price gave revenues. Geographical breakdowns into USA, Europe and the rest-of-world were used for all of these quantities. Market size was also broken into naive, experienced and late-stage patients, each of which was forecast to grow at changing rates as patients make transitions through these three classes and as future treatments improve.

Finally, a development sub-model (underlying the two double-outlined ovals in Fig. 5) produced, for each development strategy, the probabilities of development success and distributions of development costs corresponding to successful launch or failure at various stages. Costs already expended were ‘sunk’ or irretrievable under any



circumstances, so they were excluded as irrelevant to upcoming decisions. Development cash flows were combined with commercial cash flows for the NPV calculation.

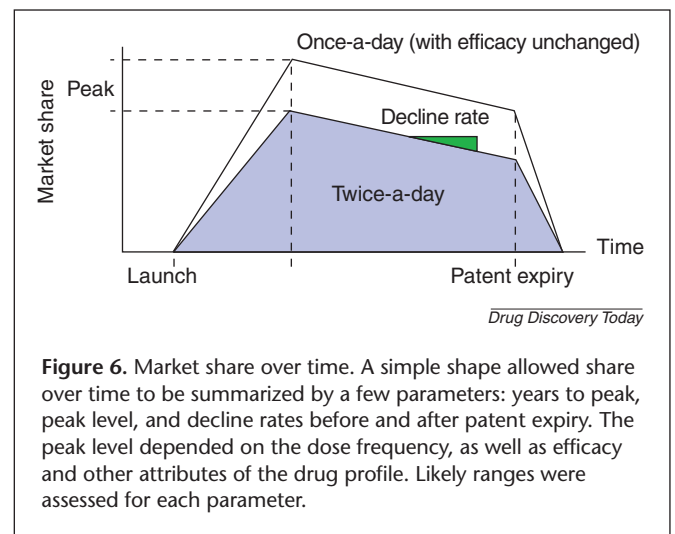
Probability distributions for the parameters were assessed in two passes. In the first pass, experts internal to the drug development company provided 10th, 50th and 90th percentiles of each continuous variable and plausible ranges for the probabilities of development success variables. Training in subjective probability assessment<sup>8</sup>, with guidance on avoiding common biases such as overconfidence, preceded the assessments. The second pass reassessed more carefully the crucial variables, as determined by a sensitivity analysis. This analysis swept each variable across its assessed range one-at-a-time to compare impacts on the value measure. Further probability assessment and modelling effort focused on the most sensitive variables. (Sensitivity analysis focused the scientific modelling effort in a similar way: for example, uncertainty in population-average adherence levels turned out to swamp uncertainty in population-average PK parameters). All assessments were documented and reviewed, with key assessments highlighted for review by senior management of the company. This helped ensure high-quality model inputs and organizational buy-in to the analytical results.

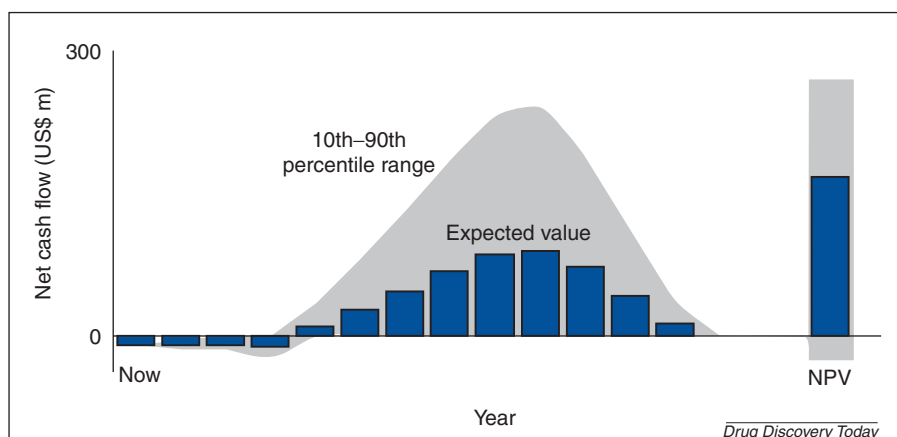
A key assessment in this case was the peak market share for each drug profile and, in particular, for once-a-day versus twice-a-day dosing. Market research indicated a significant share increase for the convenience of once-a-day dosing, depending on future competition and the development of once-a-day formulations for the other drugs in a patient's regimen. This assumed no loss of efficacy;

instead, the drug-disease model substituted a probabilistic picture of the impact on efficacy, which the economic model translated to share and NPV impacts. Figure 7 shows typical output from the economic model.

### Analysis and insights

The consultant-client team worked together to develop the strategies and models and to present several iterations of results to the company's senior management for review and guidance. Although a single large drug-disease and economic simulation could have provided distributions of value for each of the strategies, the team exploited the natural division between scientific and economic models. For example, drug-disease simulations quickly showed





**Figure 7.** Expectation and ranges of cash flows and net present value (NPV) (excluding development costs already expended) for the alternative to continue twice-a-day dose development. Scenarios with negative commercial cash flows, which occur when shares and prices are unexpectedly low, for example, result in market withdrawal decisions to limit losses. Similar plots for the other three alternatives showed higher near-term investments (initial negative cash flows) followed by potentially higher, but more uncertain commercial returns. Expected NPVs were the primary measure for comparing alternatives, but ranges were considered to clarify risks.

## Conclusion

In conclusion, a drug-disease model integrating adherence, PK and PD, together with a model of the economics of strategic alternatives, allowed complex trade-offs to be weighed explicitly, transparently and consistently. Although various models have been developed in the past for drug adherence, PK, PD and economics, it is the integration of these models that allows for maximizing value from strategic drug development decisions. For these decisions to be made well, however, the modelling tools are no more important than the R&D decision process<sup>9</sup>, which must bring together scientific and business expertise, ensure high-quality inputs and analysis, and develop a commitment by the decision-makers to act based on insights from the analysis.

that the double-dose alternatives dominated over the new formulation alternative, because the new formulation alternative was likely to provide little improvement in therapeutic coverage and long-term efficacy to counter balance its delayed launch, additional development cost and technical uncertainties.

The simulations also showed much greater sensitivity of success rates to adherence for once-a-day dosing than twice-a-day, especially for experienced patients. Therefore, an effective adherence improvement programme seemed crucial to the success of the once-a-day regimen in experienced patients. However, because of the expense and uncertain benefits of the programme, the economic model showed little likely incremental value for the alternative to combine once-a-day dosing with adherence improvement in experienced patients.

Nevertheless, the experienced patient market in the USA and Europe was much larger than the naive patient market, with the gap predicted to widen rapidly as treatments keep patients alive longer. Moreover, other companies were developing once-a-day competing drugs, which would start to erode the projected market share of the twice-a-day formulation. So, further investigation of the benefits of adherence monitoring and improvement programmes was warranted. In addition, a high value was shown for a longer-lasting formulation that would be more forgiving when patients missed once-a-day doses. This gave impetus to discovery work on a drug with an extended half-life for more effective once-a-day dosing.

## Acknowledgements

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