Drug development is time consuming, resource intensive, risky, and heavily regulated. To ensure that it makes the best drug-development decisions, Bayer Pharmaceuticals (Pharma) uses a structured process based on the principles of decision analysis to evaluate the technical feasibility and market potential of its new drugs. In July 1999, the biological products leadership committee composed of the senior managers within Bayer Biological Products (BP), a business unit of Pharma, made its newly formed strategic-planning department responsible for the commercial evaluation of a new blood-clot-busting drug. Even though Pharma's use of decision analysis began in the late 1980s, this commercial evaluation was BP's first decision analysis project. Previously, BP had analyzed a few business cases for review by Pharma. Pharma senior managers considered our recommendations relevant to their decision making. The project also institutionalized decision analysis at the business-unit level.

Drug development in the United States is time consuming, resource intensive, risky, and heavily regulated. On average, it takes nearly 15 years to research and develop a drug in the United States (DiMasi 1995) with an after-tax cost in 1990 dollars of approximately $200 million (Grabowski and Vernon 1994). Even though the results from preclinical development are imperfect predictors of clinical responses, laboratory animals remain the best practical experimental models for predicting whether a drug is safe enough to be clinically tested in humans. If the results of preclinical animal studies are favorable, a drug company can file an investigational new drug application with the Food and Drug Administration (FDA). If the FDA is satisfied with the application, then the company can choose to begin clinical development. Only half of the drugs tested in animals make it to human testing (Struck 1994). Clinical development generally consists of three phases of human testing to determine whether a drug is safe and efficacious. In Phase 1, the company tests the safety of the drug. In Phase 2, it gets the first indication of the drug's clinical efficacy in its proposed use and determines the optimum dose of the drug. In Phase 3, it confirms and expands upon the safety and efficacy data obtained from the first two phases, and the resulting data often serve as the primary basis for the FDA's approval of the drug. In parallel with its preclinical and clinical development efforts, the company develops the production process for the drug. The company starts with a supply of material from early development and upscales the process so it can meet commercial demand for the new drug in terms of quality and quantity. Based on the data it has obtained during development, the company can choose to file a biological license application with the FDA for permission to manufacture and market its drug in the United States. The FDA approves roughly one in four of the drugs tested in humans (Halliday et al. 1992). Once its drug is approved, the company is free to launch the drug in the marketplace.
To ensure that it makes the best drug-development decisions, Bayer Pharmaceuticals (Pharma) uses a structured process based on the principles of decision analysis to evaluate the technical feasibility and market potential of its new drugs. In the late 1980s through the sponsorship of the former president of Pharma, the organization adopted the dialogue decision process (Bodily and Allen 1999).

In July 1999, the biological products leadership committee composed of the senior managers within Bayer Biological Products (BP), a business unit of Pharma, made its newly formed strategic planning department responsible for the commercial evaluation of a new blood-clot-busting drug. This drug, BAY 57–9602, has reached decision point 1 (DP 1): Bayer must decide whether to begin preclinical development. BP anticipates that BAY 57–9602 will offer a new paradigm in thrombolytic drug therapy of peripheral arterial occlusion (PAO) by directly dissolving blood clots in the legs, potentially a safer or more effective treatment than those currently available. Current thrombolytic drugs are only moderately effective in dissolving blood clots in the legs and have frequent mild to moderate bleeding complications and occasional major bleeding complications.

Even though Pharma’s use of decision analysis began in the late 1980s, the commercial evaluation of BAY 57–9602 was BP’s first decision-analysis project. Previously, BP had analyzed a few business cases for review by Pharma. I needed to complete this project in three weeks so the BP leadership committee could present the recommendations to the Bayer health-care board member. With help from the leadership committee, we put together a cross-functional project team of BP employees who had decision-relevant technical and marketing expertise. The project team consisted of four research scientists, a clinician, a regulator, a production engineer, an industrial engineer, a marketer, and a decision analyst.

The BP leadership committee presented our recommendations to the Bayer health-care board member in August 1999. The board member, in turn, asked the Pharma strategic planning department to validate the evaluation. The strategic planners recommended that BP confer with additional scientific and marketing experts, internal and external to Pharma, and then present our findings to the three levels of decision-making authority within the organization. This follow-up effort took about two months.

Commercial Evaluation

Methodology and Process

Prior to the first meeting of the project team, I informed the members of their responsibilities and defined the project schedule and deliverables. Within the organization, the members of the strategic-planning department serve as internal consultants responsible for all decision analyses. Strategic planning manages the dialogue decision process, facilitates framing of the project, collects data from the technical and marketing experts assigned to the project team, constructs the financial model, and presents evaluation results and recommendations to senior managers. Members of project teams are responsible for (1) keeping their functional departments informed about the project, (2) providing the fundamental assumptions underlying their data inputs, and (3) defending these inputs to the highest level decision makers. Project teams performing commercial evaluations are essential for building support for improving the quality of decisions within the organization.

At its first meeting, the project team sought to define the purpose and scope of the project, to develop team ownership of the project, and to discuss various perspectives. At the outset of this meeting, I posed three questions: (1) Why are we doing this project, (2) What are we going to do, and (3) How will we know if we are successful? The responses formed the basis of the project mission statement:

—We want to improve thrombolytic drug therapy for PAO and we want to create value for Bayer.
—We will conduct a commercial evaluation of BAY 57–9602.
—We will consider our work successful if we deliver our evaluation on time and back it with our full consensus and if senior managers consider our recommendations relevant to their decision making.
To strengthen ownership in the project, we assigned members equal amounts of time during the first team meeting to discuss issues relative to their functional perspectives. I used brainstorming, back-casting, and role-playing techniques to uncover additional issues. I kept a list of the issues and kept it visible during the entire meeting. At the end of the meeting, I organized the issues by functional areas and categorized them as decisions (what we control), uncertainties (what we don’t control), or objectives (what we want). I then summarized the categorized list of issues to ensure that all project team members understood it completely. I further organized these issues in an influence diagram (Figure 1) and used the influence diagram as a guide for data collection.

After the first meeting of the project team, I collected data from members with expertise in technical and market specialties. Data included the time and funds needed to develop BAY 57–9602; the likelihood of BAY 57–9602 succeeding in each stage of development; the cost of manufacturing and marketing it; and the size of the PAO market and BAY 57–9602’s potential share of that market. The entire project team did not attend the meetings for collecting data. However, it met regularly to keep informed about data and assumptions and to offer different perspectives. In collecting data from experts, I (1) explained the importance of the data-collection effort, (2) defined each data input by clearly documenting its assumptions, and (3) elicited quantitative estimates from the expert for each data input. I have disguised the quantitative estimates in the paper.

Data inputs that were uncertain could be discrete, with a finite number of possible quantities (for example, preclinical development is successful or not) or continuous, with a range of possible quantities (for example, market share). I used the extended Swanson-Megill approximation (Keef er and Bodily 1983) to account for the probability distribution of each continuous random variable. This approximation results in a three-point discrete probability distribution for each continuous random variable and requires assessment of the probability of three values only (Keef er 1995). For each continuous random variable, I elicited the 10th percentile and 90th percentile from the expert, ensuring that these percentiles reflected the expert’s 80 percent confidence range. I then asked the expert whether the 50th percentile was closer to the 10th percentile or the 90th percentile and then asked for that value. For the cumulative distribution function of each continuous random variable, the extended Swanson-Megill approximation assigns a probability of 0.3 to the 10th percentile, a probability of 0.4 to the 50th percentile, and a probability of 0.3 to the 90th percentile. (Balthasar et al. 1978, Boschi et al. 1979, Merkhofer 1987, Shephard and Kirkwood 1994, and Spetzler and Staël von Holstein 1975 give details on probability assessment.)

I asked each expert to review the results to make sure they accurately reflected his or her judgment. Doing this was important because this information became part of the documentation that decision makers at the various levels considered. Documentation included definitions of the data inputs, underlying assumptions, and quantitative estimates, plus when I collected data and from whom.

**Product Target Profile**

Central to data collection is the product target profile (PTP). The PTP forms the underlying state of knowledge for assessing the technical feasibility and commercial potential of a new drug. Pharma also requires the project team to review the PTP prior to each commercial evaluation. If the PTP changes, Pharma requires collecting data anew from the functional experts. The PTP must offer at least one major competitive advantage from a patient or physician perspective (Tiggemann et al. 1998). Pharma requires that each PTP must specify how efficacious the drug will be in treating the disease, how safe the drug will be to patients taking the drug, and how convenient it will be to administer the drug to these patients. Drug administration includes the method of delivering the drug (for example, orally, inhalation, transdermal patch, intravenous injection, subcutaneous injection, or intramuscular injection), the frequency, the dosage,
Figure 1: Given the complexity and inherent structure of decisions concerning new drugs, I defined new-drug-development decision making as a sequence of six decision points with identified key market-related and scientific deliverables so senior managers can assess BAY 57-9602’s likelihood of success versus the company’s exposure to risk, costs, and strategic fit. BAY 57-9602 has reached decision point 1 (DP 1): Bayer must decide whether to begin preclinical development. After successful preclinical animal testing, Bayer can decide (DP 2) to begin testing BAY 57-9602 in humans (Phase 1). Decision point 3 (DP 3) and decision point 4 (DP 4) are both decisions to invest or not in continuing clinical development of BAY 57-9602 in Phase 2 and Phase 3. Following successful completion of development, Bayer can choose (DP 5) to file a biological license application with the FDA. If the FDA approves it, Bayer can decide (DP 6) to launch the new drug in the marketplace.

and the site (for example, a hospital emergency room, an intensive care unit, in primary care, inpatient care, or outpatient care). Pharma terminates a new drug development project if the threshold of achievement for any attribute in the PTP is not attained. Pharma does not require that the PTP include the cost of manufacture or the price.

To create the PTP of BAY 57-9602, I asked the project team to list the major benefits and drawbacks of the current standard therapy, the changes needed, and
what therapies other drug companies might be working on. I made a wish list (Keeney 1992) for BAY 57-9602 by asking team members, if you had no limitations at all, what kind of efficacy, safety, and convenience would you want BAY 57-9602 to have? I also used role playing to understand perspectives of outside stakeholders, for example, patients, physicians, and competitors. The resulting PTP of BAY 57-9602 was as follows:

**Efficacy:**
- Equal rate of blood-clot dissolution at 24 hours when compared to thrombolytic drugs.
- Equal rate of amputation at six months when compared to thrombolytic drugs.

**Safety:**
- Decreased major bleeding complications from approximately 10 to five percent when compared to thrombolytic drugs.
- Reduced febrile reactions when compared to thrombolytic drugs.
- Reduced allergic reactions when compared to thrombolytic drugs.

**Convenience:**
- Delivered intra-arterially via catheter with an infusion time < 12 hours.
- Dosage per treatment: 10th percentile of 25 milligrams, 50th percentile of 50 milligrams, and 90th percentile of 150 milligrams.
- Lyophilized vial stable at room temperature for 24 months.
- Four hours stability at room temperature when reconstituted.

**Financial Assumptions**
Pharma uses net present value (NPV) as its decision-making criterion (Figure 1). Financial data are in constant dollars. The study period is standardized at 15 years after market launch, and the risk-free discount rate, at seven percent. The tax rate is set at 40 percent. Pharma does not allocate corporate overhead costs in decision analyses of new drugs because assigning part of existing overhead to each new product inflates the cost estimates of that product and deflates its estimated profit contribution.

**Preclinical Drug Development**
Through a series of meetings, I reached agreement with the four research scientists and the clinician assigned to the project team on what animal testing would be required during preclinical development to support the clinical development plan. The research scientists estimated that preclinical development would cost about $1 million and take about 24 months (Figure 1).

I asked the research scientists to assess the probability of technical success (PTS) for preclinical development. These assessments were complicated because I asked for them in a meeting which two of the four scientists attended by video conferencing. The scientists defined preclinical-development success as the animal data showing that BAY 57-9602 is safe and efficacious. I then asked the four scientists the following back-casting questions to reduce bias: “What would cause Pharma to kill (approve) BAY 57-9602 during preclinical development?” “What would cause the FDA to believe that the preclinical animal data for BAY 57-9602 revealed an unacceptable (acceptable) safety risk to humans?” Next, I asked each scientist to write down what probability best represented his judgment that the preclinical development of BAY 57-9602 would be successful. The initial probability estimates varied from 75 to 100 percent. Each scientist explained the rationale for his probability to the other scientists. In this dialogue, the scientists showed that they had underestimated the difficulties of animal testing. I gave them the opportunity to change their probabilities. Finally, each scientist discussed his probability with the group again. The final probability estimates ranged from 60 to 80 percent (averaging 65 percent). Because the organization was reluctant to use project-specific PTS assessments, we used the Pharma PTS benchmark of 50 percent in the decision analysis and conducted sensitivity analysis with the project-specific PTS assessments. Pharma tracks the number of successful, ongoing, or terminated products it has in each stage of
development. It uses these data to derive PTS benchmarks for each stage of development. Pharma also tracks cost and time-line data for each product and derives cost and time-line benchmarks for each stage of development.

**Clinical Drug Development**

Pharma scrutinizes clinical development closely because investigational drugs are first introduced into humans at that stage, and clinical development is the most expensive stage of drug development. The Pharma strategic-planning department argued that the estimated cost of the initial BAY 57-9602 clinical-development plan that the BP leadership committee presented to the Bayer health-care board member was too low. Therefore, over the following two months the project team met with internal and external medical experts to review and update the clinical-development plan. Using information from these meetings and from previous clinical trials of thrombolysis for PAO (Ouriel et al. 1998, 1996; STILE investigators 1994), the clinician on the project team updated the clinical-development plan. Phase 1 is designed to test the safety of BAY 57-9602. Phase 2 is designed to identify the optimal dose of BAY 57-9602 to use in Phase 3. The objective or the clinical end point of the Phase 2 study is to demonstrate that the rate of dissolving the blood clot 24 hours after taking BAY 57-9602 is equal to the rate of dissolving the blood clot 24 hours after taking thrombolytic drugs. Phase 3 is a statistically designed study for proving either an efficacy clinical end point or a safety clinical end point of BAY 57-9602. To establish the efficacy clinical end point, one must demonstrate that the rate of amputation in patients six months after taking BAY 57-9602 is equal to the rate of amputation in patients six months after taking thrombolytic drugs. To establish the safety clinical end point, one must demonstrate that the rate of major bleeding complications in patients taking BAY 57-9602 is lower than the rate of major bleeding complications in patients taking thrombolytic drugs. The clinician on our project team judged that the FDA was four times more likely to require the safety end point than the efficacy end point. Pharma Strategic Planning accepted the revised clinical-development plan.

Costs for external clinical studies are based on the number of patients and the cost per patient. The clinician estimated the number of healthy volunteers needed for the Phase 1 study to be 25, the number of patients needed for the Phase 2 study to be 100, and the number of patients needed in Phase 3 to establish the efficacy end point to be 300 and to establish the safety end point to be 900. Pharma defines cost per patient as an external cost to Bayer covering clinical-investigator fees, grants, patient-participant fees, hospital care, and patient advertising. The clinician estimated that the cost per patient in Phase 2 and Phase 3 would be 50 percent more than the estimated cost per patient in Phase 1 of $10,000 since Phase 2 and Phase 3 required patients with PAO whereas Phase 1 required healthy volunteers.

In addition to an estimate of external clinical costs, Pharma requires an estimate of internal clinical costs. Internal clinical costs are for the BP clinical staff needed to support the external clinical effort. Pharma uses multipliers, ranging from 1.5 to 2.0, to determine its internal clinical costs since it believes these costs to be approximately 50 to 100 percent higher than the external clinical costs. To get away from relying on multipliers, however, it is investigating using new accounting methods to estimate internal clinical costs.

I collected estimates for the time needed to enroll patients in each study, the time to conduct each study, and the time to analyze the data and report the results. The clinician estimated the Phase 1 time line to be approximately 12 months, the Phase 2 time line to be 18 months, and the Phase 3 time line to be 30 months to establish the efficacy end point and 36 months to establish the safety end point.

The study results at each stage of clinical development determine whether a drug goes on to the next stage of development (Figure 1). At each stage of development, it can fail if data show the drug is unsafe, not well tolerated, or not efficacious. The company would then terminate development of that drug. The clinician defined Phase 1 success as the study data
showing that BAY 57–9602 is safe and well tolerated. The clinician defined Phase 2 success as the study data statistically proving the Phase 2 clinical end point of BAY 57–9602. The clinician defined Phase 3 success as the study data statistically proving the Phase 3 clinical end point of BAY 57–9602. Using these definitions of success, I assessed the probabilities of technical success (PTS) for Phase 1, Phase 2, and Phase 3 based on the clinician’s expertise. The clinician assessed the PTS values as 80 percent for Phase 1, 85 percent for Phase 2, and 85 percent for Phase 3. The BP leadership committee found these assessments too optimistic compared to Pharma PTS benchmarks (75 percent for Phase 1, 50 percent for Phase 2, and 75 percent for Phase 3). Since the senior managers seemed more comfortable with the Pharma PTS benchmarks than with project-specific PTS assessments, I used the PTS benchmarks for Phase 1, Phase 2, and Phase 3 in the decision analysis and conducted sensitivity analysis with the project-specific PTS values.

Production Process Development
The cost of goods is a function of direct labor costs, material costs, plasma cost, the costs for supplies, shipping, and testing, capital depreciation, and the number of treatments (Figure 1). In addition, direct labor costs, material costs, and plasma cost depend on the yield of the production process; higher yield results in lower direct labor costs, material costs, and plasma cost. Plasma cost is also a function of dosage per treatment; a lower dose results in lower plasma cost. I collected probability estimates from the industrial engineer assigned to the project team on the yield for the production process. He also provided estimates for direct labor costs, material costs, plasma cost, and the costs of supplies, shipping, and testing. Pharma depreciates capital using the 15-year straight-line method. Pharma assumes that the capital investment for the production facility occurs approximately five years before the anticipated launch date of the new drug to allow for engineering, construction, validation, and FDA approval of the facility. The production engineer on the project team estimated the capital investment required for a production facility and the cost of developing the commercial production process for BAY 57–9602.

Regulatory Approval and Orphan-Drug Status
I obtained data on the time the FDA would take to review the biological license application for BAY 57–9602 from the regulator assigned to the project team, and I used the Pharma PTS benchmark of 90 percent for regulatory approval (Figure 1). Because the need for safer and more effective thrombolytic drugs in PAO is apparently high, fast-track review of the biological license application for BAY 57–9602 is possible. The US government passed fast-track legislation to facilitate development and expedite review of drugs that demonstrate the potential to address unmet medical needs in the treatment of serious or life-threatening conditions. According to the regulator, BAY 57–9602 must obtain fast-track submission before receiving a fast-track review of the biological license application (Figure 1). She believed that the probability of BAY 57–9602 obtaining fast-track submission was 75 percent. If BAY 57–9602 obtained fast-track submission, she estimated that the FDA could review the biological license application in six months or in 12 months. She also estimated the probability of a six-month review was 60 percent and the probability of a 12-month review was 40 percent. If BAY 57–9602 did not obtain fast-track submission, she estimated the FDA would take 24 months to review the biological license application. I obtained these probability assessments from the regulator via teleconference.

BAY 57–9602 could be eligible for orphan-drug status (Figure 1). The US government passed orphan-drug legislation to encourage development of drugs to treat serious or life-threatening diseases that affect fewer than 200,000 patients and have no effective cure or treatment. FDA-approved orphan drugs receive a seven-year period of market exclusivity in the US (10 years in Europe) guaranteeing that no other drug may be approved for the disease unless it demonstrably provides better efficacy or safety. Based on the regulator’s judgment, I assessed the probability of BAY 57–9602 obtaining orphan-drug status to be 75 percent.

Marketing
Launching a new drug in the marketplace with the goal of achieving maximum penetration and exposure
is an expensive advertising and public relations effort. It requires making sales visits to physicians, hosting medical advisory meetings, sending representatives to symposia, providing press releases, and conducting post-marketing studies. Estimating the cost of such efforts depends largely on estimating the number of physicians who would administer the drug. For example, Bayer estimates that the marketing cost for BAY 57-9602 would be less than the marketing cost for an asthma drug since fewer physicians treat PAO than treat asthma. The clinician and the marketer assigned to the project team decided that interventional radiologists and vascular surgeons and some general radiologists would administer BAY 57-9602 to treat PAO. As is standard in most Pharma DP 1 commercial evaluations, I assumed BAY 57-9602 would be launched in eight countries: the United States, Canada, France, Germany, Italy, Spain, the United Kingdom, and Japan.

Pharma Strategic Planning challenged the initial marketing-cost estimates that the BP leadership committee presented to the Bayer health-care board member as too low. Over the following two months, the project team discussed these estimates with Pharma marketing experts and compared them to audits of hospital sales of thrombolytic drugs currently marketed in the United States. Based on our detailed review, Pharma Strategic Planning accepted our revised marketing cost estimates (Figure 2).

**Size of the PAO Market**

I obtained data on the size of the PAO market from the marketer on the project team. In 1998, about 110,000 patients were hospitalized for PAO in the United States. Since similar data for Canada, Europe, and Japan were not available, the marketer estimated that the number of PAO patients in these regions would be proportional to the rates for the incidence of peripheral vascular disease in those countries. I did not collect probability estimates on the number of PAO patients per year because of practical limitations. Instead, I collected probability estimates from the marketer for the annual growth rate of patients with PAO (Figure 1). For the 10th percentile, she assumed that an increase
in anti-atherosclerotic techniques would result in a decrease in the annual growth rate of one percent. For the 50th percentile, she assumed an annual growth rate of one percent for patients with PAO. At the 90th percentile, she assumed an increase of three percent because of unhealthy lifestyles (for example, insufficient exercise or failure to take cholesterol-reducing medications) and the aging of the population. She estimated that the typical PAO patient could receive one thrombolytic drug treatment per year and one out of four patients could receive two treatments.

Class Share and Product Share in the PAO Market

There are two classes of treatment for PAO: thrombolytic drugs and surgery. Currently, more than half of PAO patients in the US receive thrombolytic drug therapy instead of the surgical procedures (for example, thrombectomy, angioplasty, bypass graft, mechanical reperfusion, or leg amputation), whereas fewer than half of PAO patients in Europe and Japan receive thrombolytic drug therapy. If the thrombolytic drug therapy is ineffective, surgery is performed. As better thrombolytic drugs become available, use of thrombolytic drug therapy should increase, particularly in Europe and Japan.

The marketer estimated the current share of the thrombolytic drug class for the United States and Canada (80 percent), Europe (40 percent), and Japan (25 percent). She believed that use of thrombolytic drugs for treating PAO patients would likely increase over the next five to 10 years, so I asked her to estimate the future peak share of the thrombolytic drug class in the PAO market (Figure 1). These estimates ranged from a 10th percentile of 70 percent to a 90th percentile of 95 percent (50th percentile of 85 percent) for the United States and Canada, 25 to 75 percent (50th percentile of 50 percent) for Europe, and 20 to 70 percent (50th percentile of 30 percent) for Japan. For the 10th percentile, she assumed a future decrease in thrombolytic drug therapy because of improved surgical methods; at the 50th percentile, she assumed a modest increase in future thrombolytic drug therapy; and at the 90th percentile, she assumed a significant increase. The distribution spreads for Europe and Japan are wider for the United States and Canada because the marketer was more familiar with the PAO markets in the United States and Canada than with the markets in Europe and Japan.

The products in the thrombolytic drug class that are marketed for treating PAO are called plasminogen activators. All plasminogen activators work by the same mechanism and thus have the same limitations in efficacy and complications of bleeding. BAY 57–9602 works by a different mechanism and is expected to lack these limitations, giving it a sustainable competitive advantage over plasminogen activators.

Using time-line estimates for preclinical development, Phase 1, Phase 2, Phase 3, and regulatory approval of the biological license application, I determined the 10th, 50th, and 90th percentiles for the launch year of BAY 57–9602 in the United States and Canada (Figure 1). I assumed the launch date of BAY 57–9602 in Europe would be one year later and in Japan, two years later. Based on these launch estimates and the R and D activity of other pharmaceutical companies, the project team expected BAY 57–9602 to be the first product of its type available in the thrombolytic drug class for treating PAO.

The marketer estimated the peak share BAY 57–9602 could obtain in the thrombolytic drug class for the United States and Canada, for Europe, and for Japan. For the United States and Canada, her estimates ranged from a 10th percentile of 30 percent to a 90th percentile of 75 percent (50th percentile of 45 percent). For Europe, the 10th percentile was 25 percent and the 90th percentile was 65 percent (50th percentile of 40 percent). For Japan, the 10th percentile was 20 percent and the 90th percentile was 50 percent (50th percentile of 30 percent). For the 10th percentile, she assumed a slow uptake of BAY 57–9602 in the thrombolytic drug class, for the 50th percentile she assumed a modest penetration of BAY 57–9602, and for the 90th percentile she assumed significant penetration.

Even though the R and D activity of other pharmaceutical companies did not indicate that a competitor would launch a similar product, the project team considered the possibility of a competitor launching a product similar to BAY 57–9602, a me-too competitor. I asked the marketer to estimate the probability that a me-too competitor could enter the PAO market and to
estimate its potential impact on BAY 57–9602’s share of that market. For the 10th percentile, she assumed a me-too competitor would launch one year after BAY 57–9602 and estimated that BAY 57–9602 would lose 40 percent of its share. For the 50th percentile, she assumed a me-too competitor would launch three years after BAY 57–9602 and estimated that BAY 57–9602 would lose 30 percent of its share. For the 90th percentile, she assumed a me-too competitor would launch four years after BAY 57–9602 and estimated that BAY 57–9602 would lose 25 percent of its share. If BAY 57–9602 was to obtain orphan-drug status, the marketer believed that BAY 57–9602 would lose 20 percent of its market share to a me-too competitor after market exclusivity expired.

The project team also considered competition from recombinant technology (Schmidt 1996) during the product life cycle of BAY 57–9602. The marketer made probability estimates as to when a recombinant competitor could enter the PAO market and what its impact could be on BAY 57–9602’s share of that market. For the 10th percentile, she assumed a recombinant competitor would launch its product four years after Bayer launched BAY 57–9602; for the 50th percentile, she assumed six years; and for the 90th percentile, she assumed eight years. With a recombinant drug competing in the PAO market, BAY 57–9602’s loss in market share ranged from a 10th percentile of 50 percent to a 90th percentile of 80 percent (50th percentile of 60 percent). The marketer estimated the probability of a recombinant competitor entering the PAO market to be approximately 20 percent. The time BAY 57–9602 and its competitors would take to ramp up from launch to peak product share ranged from a 10th percentile of three years to a 90th percentile of six years (50th percentile of five years).

**Pricing**

Treating PAO is expensive. Current thrombolytic drug therapy takes approximately 24 hours and requires several trips to the radiology suite for X-rays and a stay in a critical-care unit. In the United States, the cost for thrombolytic drug therapy for PAO (Neudeck et al. 1997) is approximately $2,000 to $4,000 whereas the cost for PAO surgery is approximately $22,000. The marketer assumed the cost of thrombolytic drug therapy in Canada to be the same as the cost in the United States, and she assumed the cost in Europe was approximately half the cost in the US and the cost in Japan was three-fourths that in the US. The marketer believed that BAY 57–9602 could command a 20 percent premium over the current thrombolytic drug therapy.

Since the marketer did not believe that BP could control the price of BAY 57–9602, I modeled price per treatment as an uncertainty rather than a decision (Figure 1). Pharma commonly considers the price for early-stage-development drugs to be uncertain in DP 1 evaluations.

Pharma Strategic Planning challenged the initial probability estimates of price that the BP leadership committee presented to the Bayer health-care board member as too high. Over the following two months, the project team discussed our assumptions that BAY 57–9602 would command premium prices with Pharma marketing experts. I then asked the marketer for her probability estimates on the price per treatment in the US, Canada, Europe, and Japan. For the 10th and 50th percentiles, she assumed no price premium; for the 90th percentile, she assumed a price premium. Pharma Strategic Planning accepted these new estimates.

**Evaluating the Results and Generating Insights**

I determined the key drivers of NPV by varying each data input over its range of estimated values while leaving the other inputs set at their estimated base-case values (Figure 3). I selected the following variables as key drivers of NPV because they represent over 90 percent of the uncertainty in NPV (Poland 1999): peak product share of BAY 57–9602 in the thrombolytic class for the US, price per treatment of BAY 57–9602 in the US, annual growth in the number of patients with PAO, the impact on BAY 57–9602’s market share from a recombinant competitor, the probability of BAY 57–9602 obtaining orphan-drug status, R and D costs, and the launch timing of a me-too competitor. I also included the probability of a recombinant competitor entering the PAO market because one of the key drivers was the impact on market share from a recombinant
I also considered the probabilities of technical success for preclinical development, Phase 1, Phase 2, Phase 3, and regulatory approval to be key drivers of NPV because Pharma would terminate BAY 57–9602 if it failed in any of these stages.

The BP leadership committee and the project team were surprised that the launch date of BAY 57–9602, investment in a production facility, and the factors influencing cost of goods (dosage per treatment and production process yield) were not key drivers of NPV (Figure 3). I attributed the low impact of launch date to the assumption that BAY 57–9602 always preceded competing similar products in the PAO market (the me-too and recombinant competitors). Every year BP submits a five-year budget plan to Pharma for its approval. In determining the budget, Pharma scrutinizes proposed capital investments carefully and BP therefore expected the capital investment for BAY 57–9602 to be a key driver. And because BP manufactures its own drugs, it is keenly aware of the cost of goods.

I modeled the key drivers probabilistically. For those that were continuous random variables, I used the extended Swanson-Megill approximation (Keefer and Bodily 1983). I set non-key drivers at their estimated base-case value. The key drivers modeled probabilistically resulted in a sequential decision tree with 1,955 possible NPV paths, including technical risk at each development stage and market risk (Figure 4). I also ran the model with only market risk considered, assuming technical success at each stage of development (Figure 5). In making go-no-go decisions, the decision makers at various levels within Pharma compare the probability-weighted averages for each drug-development project with the averages for the other Pharma drug-development projects. The probability-weighted averages for BAY 57–9602 (Figures 4 and 5)
compare favorably to similar early-stage development drugs in Pharma’s portfolio. However, when I set the peak product share of BAY 57–9602 in the thrombolytic class for the US at its 10th percentile, the probability-weighted averages became unattractive. The remaining key drivers (Figure 3) had little impact on the probability-weighted averages.

The estimates for R and D cost were controversial because they were lower than the Pharma benchmarks. BP argued that the benchmarks were based primarily on pharmaceuticals and therefore were not comparable to biologics with their different development processes. Pharma, however, argued that its benchmarks included biologics and were audited cost figures while the costs for BAY 57–9602 were estimates. Since BP did not have its own cost benchmarks, it could not argue persuasively with Pharma. I did not want to underestimate the R and D costs since this would invalidate
the results of my analysis and any recommendations based on it. To circumvent this impasse, we determined the sensitivity of R and D costs by considering the case in which the R and D cost estimates for BAY 57-9602 would be the same as the Pharma R and D cost benchmarks. The results showed that the benchmarks had little impact on the probability-weighted averages. BP is developing its own R and D cost benchmarks.

**Conclusion**

The project team presented our input assumptions and recommendations for the DP 1 commercial evaluation of BAY 57-9602 to the three levels of Pharma decision makers. In November 1999, the BP leadership committee awarded DP 1 status to BAY 57-9602. In December, the Pharma international committees of senior managers awarded DP 1 status to BAY 57-9602. In January 2000, BP began preclinical development of BAY 57-9602.

The evaluation results the BP leadership committee presented to the Bayer health-care board member in August differed from the results presented to the three levels of decision makers in November and December. Even though the probability-weighted averages (Figures 4 and 5) became less favorable with the lower price assumptions and higher cost estimates for R and

**Figure 5:** This cumulative risk profile illustrates market risk of BAY 57-9602, assuming technical success for each development stage. The probability-weighted average for BAY 57-9602 compares favorably to those for similar early-stage development drugs in Bayer Pharmaceuticals' portfolio. The downside market risk is relatively low (20 percent chance of losing money) whereas the upside potential is high.
D and marketing, Pharma still found the results attractive compared to its other DP 1 drug-development projects. External validation of the data inputs and assumptions demonstrated their rigor and defensibility. Senior managers could compare the evaluation results for the BAY 57-9602 with those for other development drugs with confidence. The international committees lauded the project team's effort as top notch, and the decision analysis for BAY 57-9602 set new standards for subsequent BP analyses.

Acknowledgments
The author thanks the associate editor and two reviewers of Interfaces for improving the quality of this manuscript. He also thanks the associate editor and two reviewers of Operations Research, Craig Kirkwood, and Kimberly Stonebraker for reading earlier drafts. Finally, the author thanks Mary Haight, whose editing greatly improved the paper's readability.

References


David G. Spencer, Ph.D., Vice-President, Respiratory/Critical Care Life Cycle Management, Biological Products, Bayer Corporation, Post Office Box 13887, 85 T.W. Alexander Drive, Research Triangle Park, NC 27709, writes: “I have reviewed your manuscript and returned my comments to you previously. I believe that this paper accurately represents our use of decision analysis in general and also specifically with regard to Bay 57-9602. In long-term, high-risk activities like drug development, there is no substitute for this sort of approach to support decision making. Cost inputs, judgements of potential outcomes, and the assignment of probabilities help to place a project's potential contribution within a portfolio. They also help identify key variables (sensitivity analysis) for special attention by the project team and management going forward, due to the disproportionate contribution of those variables to the value of the project.

“Appropriate application of this methodology has allowed us to make better decisions about how to develop this drug—which indication, which clinical strategy, which target market benefits. Increased confidence thus derived supports uniform commitment by the company during development.”