

Modelling of the biopharmaceutical drug development pathway and portfolio management

Anuradha Rajapakse, Nigel John Titchener-Hooker, Suzanne S. Farid*

*The Advanced Centre for Biochemical Engineering, Department of Biochemical Engineering,
University College London, Torrington Place, London WC1E 7JE, UK*

Available online 8 March 2005

Abstract

Given the time, cost and risk associated with drug development, biopharmaceutical companies typically need to have a portfolio of drugs in development to be successful. Current pressures of cost and speed to market are driving the need for more effective means of assessing the value and risks of such drug portfolios. This paper presents research to generate a prototype computer tool developed to predict the process and business outcomes for portfolios of biopharmaceutical drugs proceeding through the development pathway. The tool incorporates the interactions between drug development activities and the available resources. In addition to the business and process issues, the risks involved in the process of drug development have also been incorporated into the model. A case study is presented to illustrate how the tool can be used to assist business decisions regarding biopharmaceutical portfolio management. The example addresses scenario analysis and the question of outsourcing versus in-house manufacture of material for clinical trials and the market under uncertainty.

© 2005 Elsevier Ltd. All rights reserved.

Keywords: Biopharmaceutical drug development; Computer-aided simulation; Portfolio management; Risk; Decision-support tool

1. Introduction

The rapid growth of the biotechnology industry as the backbone of high technology, highly specific and effective new medicinal therapies have had a profound effect on the pharmaceutical industry. The ability to genetically modify living organisms to produce a range of medicines has contributed to a plethora of biopharmaceuticals being developed. In 2000, 28 major protein-based products generated US\$ 13.3 billion of sales and in 2002, there were 99 protein-based therapeutics in Phases III and II clinical testing (Ginsberg, Bhatia, & McMinn, 2002). However, the process of bringing these products to the market is a costly and risky business. On average it takes 7.7 years to bring a biopharmaceutical product to market (Foo, Karri, Davies, Titchener-Hooker, & Dunnill, 2001) and costs over US\$ 800 million and this cost of research and development (R&D) for new drugs has been on the rise for the past two decades (DiMasi,

Hansen, & Grabowski, 2003). Given the uncertainty associated with drug development, biopharmaceutical companies typically require a pipeline of drugs constantly to remain in business. Speed to market and pressure to reduce costs are critical factors driving the need for more effective means of assessing the value and risks of such drug portfolios. Various methods are used by the pharmaceutical industry for product portfolio management. Popular financial models used by companies include net present value (NPV), decision trees option models and computer simulations (Soegaard, 2003). Non-financial models, used to a lesser extent, comprise standard strategic models, risk-reward charts and scoring models (Soegaard, 2003).

Managing an R&D portfolio is complicated by constraints on budget, personnel and available capacity and how best to deploy these resources. Each drug is also subject to technical and commercial uncertainties. Technical uncertainties include the risk of failure during each phase of clinical testing; market uncertainties include the volatility in the forecasted demands and prices of drugs as well as the impact of competition. Given these factors the survival of a company can

* Corresponding author.

E-mail address: s.farid@ucl.ac.uk (S.S. Farid).

depend on the key decisions made during the development of each drug within a portfolio.

Portfolio selection and capacity planning problems have been addressed in process engineering literature. Mathematical methods have been applied for the resource constrained scheduling of testing of new product development (Jain & Grossmann, 1999) and optimisation of new drug candidate portfolio under resource constraints (Subramanian, Pekny, & Reklaitis, 2000). Rogers, Gupta, and Maranas (2002), presented a real options based analysis of selecting R&D portfolios. Gatica, Papageorgiou, and Shah (2003) presented a mathematical programming method for capacity planning under uncertainty for the pharmaceutical industry and Levis and Papageorgiou (2004) outlined a mathematical approach programming approach for long-term, multi-site capacity planning under uncertainty in the pharmaceutical industry. Here, the approach used was to select the optimum portfolio from a given set of candidates and planning of the manufacturing schedules under constraints. Levis and Papageorgiou (2004) also provide a good review of the papers presented on mathematical approach to the problem of portfolio optimisation and task scheduling. However, these usually result in complex mathematical methods where a high level of knowledge is required for application. Such methods have been applied mostly to chemical entities and agro-chemicals. By contrast little attention has been paid to biopharmaceuticals.

The need for computer-aided simulation tools, capable of capturing the technical and business aspects of drug development as well as the risks, is critical for such decision-making (Karri, Davies, Titchener-Hooker, & Washbrook, 2001). The use of a prototype decision-support tool for controlling the cost of goods in biopharmaceutical manufacture under uncertainty has been demonstrated (Farid, Washbrook, & Titchener-Hooker, 2001; Mustafa et al., 2004). However, the impact of manufacturing decisions on development timelines and costs was not explored. Accurately computing the uncertainties inherent in product development poses the biggest challenge of all, creating difficulties in comparing and prioritising projects in development (Soegaard, 2003). This paper presents research to generate a prototype computer-aided tool to predict the outcomes of employing different development strategies for a portfolio of biopharmaceutical drugs proceeding through the development pathway. It seeks to quantify the outcomes in the form of simple economic metrics such as the NPV, which may be used as the basis for decision-making.

1.1. Benefits and challenges of portfolio management

High quality decisions about long-term business strategy often require the explicit analysis of uncertainty. Portfolio management is an established business process that is linked with other business processes including strategic planning and budgeting. Through portfolio management, decision-making and resource allocation are measurably improved.

Keelin and Shew (2003) state that portfolio management is justified by a 100-fold return on investment.

Traditional portfolio evaluation models often rely on qualitative and semi-quantitative tools. New quantitative methods have been developed that compute directly how much value decisions add to a R&D portfolio (Keelin & Shew, 2003). Portfolio management applies to all areas of drug development. The decisions include which targets should be pursued at the point of drug discovery through to deciding on the appropriate level of manufacturing capacity needed, and finally to which areas of the market have to be captured. High quality valuation methods have to be applied to capture the risks and rewards implicit in applying different options in R&D projects. By being able to compute and then compare the array of possible outcomes and key sources of uncertainty, management is provided with a key tool to manage and balance the portfolio. Effective portfolio analysis can identify the optimal portfolio in terms of value creation for any given set of constraints.

1.2. Modelling biopharmaceutical drug development

Modelling the drug development process enables the interactions between the different tasks involved and the resource demands at different stages of development activities to be captured and quantified. Bioprocess modelling has been used to explore different process routes and assist decision-making with much success (Farid, Novais, Washbrook, & Titchener-Hooker, 2000; Lim, Washbrook, Titchener-Hooker, & Farid, 2004; Mustafa et al., 2004). Modelling of the drug development process is not presented much in the literature. However, Luehrman (1994) describes a model configured to assess the risks and returns of new projects. Karri et al. (2001) presented a hierarchical framework to assist decision-making in the biopharmaceutical industry while Stonebraker (2002) presents a model of a single project aimed at evaluating its commercial worthiness.

When modelling biopharmaceutical development the challenge is to model effectively the many different tasks involved in taking a drug through the phases of drug development, which increase in complexity and duration as the drug approaches the market. The company- and drug-specific business and process characteristics all have to be captured successfully and the resulting model be able to compute the time-to-market, cost, revenue and the risk, which all feature in the decision-making process. Simulating a portfolio of drugs and their development activities provides management with the capacity to explore, *in silico*, different strategies and to use the insight gained to make real-life decisions that would add value in both the short and long-term to the portfolio.

A typical example might be that the early planning of development tasks and the appropriate allocation of resources will help the company to identify resource bottlenecks and act upon them early. A tool that combines the biopharmaceutical drug development activities (e.g., process development, manufacturing and the clinical trials, etc.) and the resource flows

(e.g., cash, facilities, personnel, etc.) has not been presented in the literature. The ability to model and evaluate the impact of process and business options within a company could greatly enhance decision-making and improve the economics of new drug development (Karri et al., 2001). The software approach detailed in this paper would be useful in a company for ensuring adequate linkage between process and business decisions. An example would be the choice of manufacturing route to adopt, e.g., in-house versus contract manufacturing, and the implications of this on the key performance metrics.

1.3. Paper layout

The remainder of the paper is structured as follows. In Section 2, the design methodology of the tool architecture is outlined, providing a brief introduction to the modelling approach and its implementation in a hierarchical task-oriented framework. The key input and output parameters of the model are identified. A case study is then presented to illustrate specific capabilities of the tool that can aid decision-making with regards to a manufacturing strategy (Section 3). Finally, a conclusion is provided in Section 4.

2. Design methodology

A computer-aided tool capable of capturing the risk and the rewards of different strategies can help provide a ratio-

nal basis for confident decision-making in biopharmaceutical drug development planning and portfolio management. The next section outlines the modelling approach taken in developing this decisional tool.

2.1. Modelling approach

A structured model of the biopharmaceutical development pathway was used in order to facilitate rapid modelling of the impact of business and process decisions made during the management of biopharmaceutical product development on the portfolio profitability. The tool seeks to integrate various aspects, including resource management and the development and manufacturing activities required for clinical trials as each relate to strategic decision-making. The tool structure was arranged in a hierarchical manner to represent the key tasks of the biopharmaceutical drug development process through a series of levels increasing in complexity (Fig. 1). The hierarchical structure enables the user to prototype a management strategy at the required level of detail, for example a high level for executive decision-making and a lower level for process decision-making. In addition it enables a series of ‘what-if scenarios’ rapidly. It also allows the user to access a breakdown of the model outputs. Therefore, the costs and durations of specific tasks (e.g., cost and duration of Phase I clinical trials) are available for analysis or comparison. The hierarchical task representation also provides the flexibility to extend the task tree further without compro-

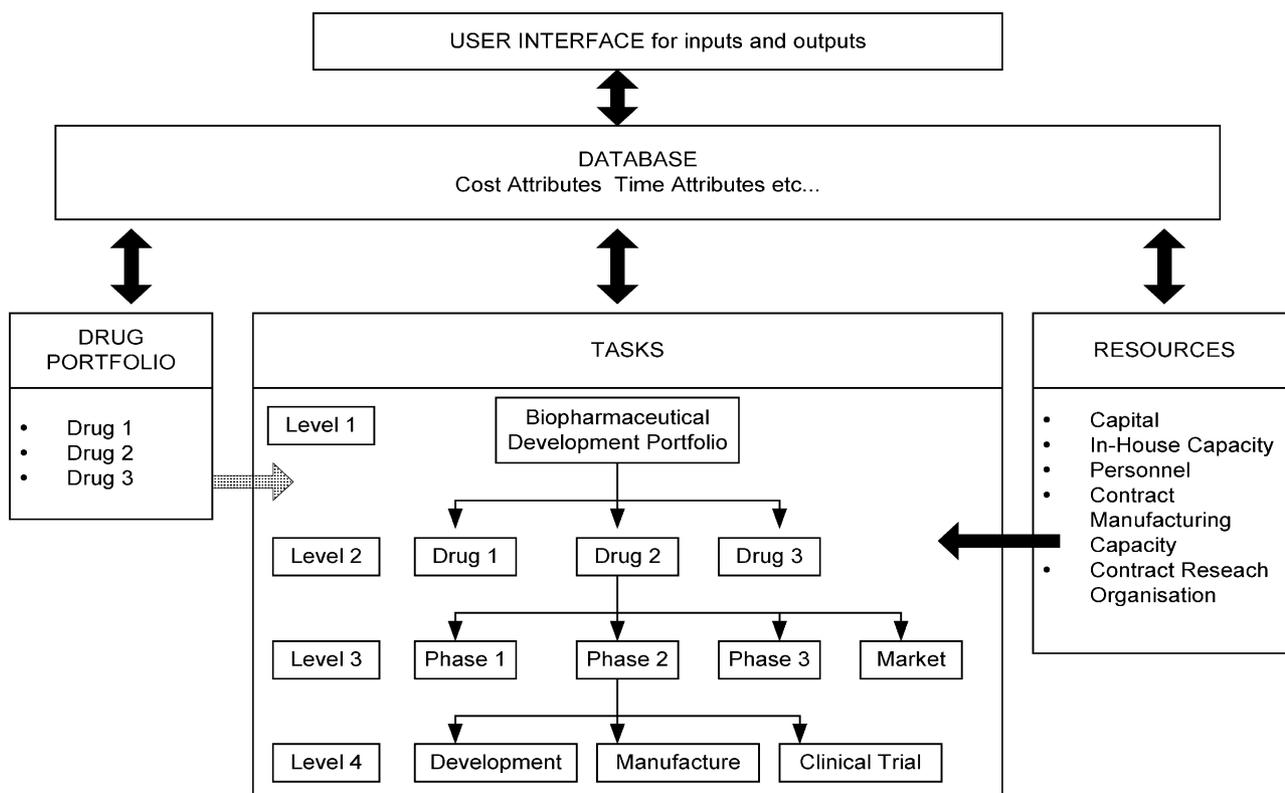


Fig. 1. Simplified schematic of the main components of the tool.

mising tool functionality; that is the modular and extensible nature of the tool permits new blocks to be added to model a particular activity in greater detail without affecting the code at higher levels.

A similar approach has recently been employed to model the manufacture of biopharmaceuticals (Farid et al., 2000, 2001; Lim et al., 2004; Mustafa et al., 2004). The software tool comprises the tasks involved in taking a drug to the market (e.g., development work, manufacture, clinical trials) and the resources required to carry out each task (e.g., capital, in-house capacity, personnel, contract manufacturing capacity). At the top-most level of the tasks, the portfolio of drugs is modelled, which then breaks down into the projects handling individual drug candidates. At a greater level of detail, the three phases of development and the market features are modelled for each drug.

As depicted in Fig. 1, the tool includes the development process, manufacture and clinical trials associated with each phase. For each of these activities, a series of decision points was defined and relevant attributes assigned. As illustrated in Fig. 1, the tool captures the interaction between the drug development tasks and the resources required for each drug in the portfolio. In addition, the attributes are stored in a database that the user can access. Default values for task durations and costs, as well as risks of failure are provided as part of the knowledge repository.

The aim of the tool is to assess all the possible situations using Monte Carlo simulations. Once the possible outcomes have been generated, decisions could be made based on these results. The results would show whether the strategy being examined is of high risk or low reward, etc. The tool is not expected to optimise the strategy but to show all the possible outcomes regarding decisions in the management of the process of drug development, which will allow the decision makers to have an informed conversation about the possible choices.

2.2. Implementation

For the design, implementation and application of the generic tool, data for a portfolio of monoclonal antibodies progressing from Phase I development through to the market was used. The model was run to simulate a time period of

20 years from discovery for each drug and was developed using a task-oriented approach on the platform of the visual simulation package Extend Industry Suite v5 (Imagine That Inc., San Jose, USA). Extend uses discrete-event simulation, enabling the dynamic nature of drug development decisions to be captured.

Specific blocks to simulate the tasks and resources were coded in Extend and linked to represent the whole development process within the portfolio. Each of the tasks was simulated as an activity requiring resources. Each drug was then modelled as an item progressing along the development pathway undergoing different tasks such as development or manufacture for which specific attributes were set (e.g., costs, time). During a simulation, a resource remains in the queue and is only released when there is a sufficient quantity available in the resource pool to meet the requirement.

An Excel spreadsheet was used as the database for the setting of parameters and receipt of calculated variables from the simulations. The data to populate the model was obtained from literature, a database of biopharmaceuticals built at UCL (Foo et al., 2001) and industrial experts. Upon execution, the simulation ran to develop the drugs using the resources (capital and personnel) available. The impact of implementing different strategies for the management of the portfolio was investigated. These strategies included deciding priorities for drug development or deciding whether to manufacture in-house or use a contract manufacturer.

The risks involved in the process of drug development were incorporated into the model. Technical uncertainties included the risk of failure due to there not being an economically feasible process route and the failure at the end of each phase of clinical testing. Monte Carlo simulations were used to imitate the uncertainties in drug development such as random failure of drugs and the market uncertainties, which include the volatility in the forecasted demands and the likely selling price of the drugs.

2.3. Key parameters

Table 1 shows the input parameters provided to the model and the processed outputs. Estimations of the drug development data such as the number of personnel needed for the

Table 1
Input/output parameters for the model

Drug-specific	Task-specific	Resource availability	Portfolio
(a) Input parameters			
Resource requirement	Batch cost	Personnel	No. of drug candidates
Estimated dose levels	Batch duration	Production facilities	
Clinical trial data	Production personnel required	Capital	
Success probability			
Market data			
(b) Output parameters for the model			
Develop't cost breakdown	R&D cost and time	Utilisation profiles	Cost distribution
Time to market	Manufacturing cost and time		NPV distribution
	Clinical trial cost and time		Risk
			No. of drugs into the market

development work was entered along with the probability distributions of uncertain parameters. At the beginning of the simulation, the resource levels available were specified. The outputs of the model included the cost of developing the drug portfolio and the time to market. The cost analysis was extended to include other profitability indicators such as the NPV. NPV calculates the current value of a future cash flow and is a very useful metric for the comparison of the current costs required to undertake a project versus the potential benefits, in this case revenues, which the project will yield some time in the future. Consequently, using this tool the users can perform strategic, tactical and operational analysis according to their particular goals.

The graphical representation of the model components provides a high degree of user interaction, enabling a clear visualisation of various development stages and offers a comprehensive view of the simulation application. The adoption of a hierarchical form of representation enables rapid prototyping of new models in an organised and systematic manner. Whenever a simulation is run, the model is animated to enable the user to view the occurrence of events at any given point in time. Animation features enable the visualisation of the flow of items (e.g., drug candidate) throughout the simulation run and aids in the debugging process for the developer. The use of discrete-event modelling allows the capability to view the time-based behaviour of the system and makes it possible to track the values of time-dependent parameters such as cost and resource usage (Lim et al., 2004).

3. Case study

A hypothetical case study that examines the use of the tool to plan and manage the development of a biopharmaceutical drug portfolio is presented next. The example is based on a company that has three potential products, all monoclonal antibodies (MABs), in its portfolio that are ready to go into clinical development. Although all three drugs are MABs, they are of different therapeutic classes with differences in the doses and the market sizes. This allows the portfolio to be diverse and makes the decisions relevant and challenging. The company was modelled as a small to medium size organisation, which had finite resources and a defined manufacturing capacity.

3.1. Set-up

To evaluate the functionalities of the software tool, the progress of three monoclonal antibodies from discovery to the market were simulated (Table 2). This is a necessarily small sample selected so as to provide confidence in the simulation outputs and to illustrate the type of data that can be generated. Data from public domain sources, literature (DiMasi et al., 2003; Farid, 2001; Reichert, 2001) and expert knowledge was used for this base case simulation. The drugs used in this case study have been modelled as breakthrough drugs in their therapeutic areas.

Table 2
Description of the drugs in the portfolio (Farid, 2001)

Drug	Drug characteristics			
	MAB type	Dose	Therapeutic area	Market size
1	Chimeric	Low	Clot prevention in PTCA	High
2	Humanized	Medium	Breast cancer	Low
3	Chimeric	High	Crohn's disease	Medium

3.1.1. Sensitivity analysis

Since there are many parameters to be considered in the development of a drug, the tool was used to find out which parameters had the most effect on the NPV of the portfolio. Each input was varied in turn while keeping the others constant (Table 3). The percentage change in NPV relative to the base case value was evaluated to highlight the key factors to be considered when allocating resources and planning in the process of drug development.

3.1.2. Scenario analysis

A series of simulations were performed to illustrate the application of the tool to perform scenario analysis. In each of these, two parameters were changed simultaneously so as to study the effect of a combination of inputs on the portfolio.

Process efficiency and time spent in development: The first scenario considered the time spent in process and product development and the improvements in yields achieved. The negative effects of process development delays can only be felt later if and when the drug gets into the market and fails to recover the money invested. The impact of varying the time spent in development and the associated yields achieved on the NPV was recorded. The results were plotted on a two-dimensional surface diagram to show how time in development and yields need to be balanced if an improved NPV is to be achieved.

Manufacturing time and dose fluctuations: The analysis was extended to include uncertainty in the estimated dose levels and the manufacturing time of product for clinical trials. In the initial assessment of a new drug candidate, a series of estimates are made by experts in each field to predict its value to the portfolio (Stonebraker, 2002). The dose levels required would initially be estimated by clinicians and con-

Table 3
Percentage changes made to the different parameters from the base case values

Input	Percentage change to base case
Market population captured	±50
Drug price set	±20
Time spent in process development	±50
Clinical trial time	±50
Personnel available for process development	±50
Presence of a competitor	+25
Mass per batch (in-house production)	±50
Quantity of material (production outsourced)	+100/−50
Contract manufacturing time	±50
Quantity of material (in-house production)	+100/−50

firmed towards the end of Phase II clinical trials or even as late as Phase III trials. Therefore, manufacturing activities have to be planned according to the estimated dose levels and patient numbers needed for clinical trials.

Having the capacity to predict the effect of fluctuations in dose levels of one drug or all the drugs in the portfolio as a whole provides valuable data on which to plan. Such a scenario also relates to the occurrence of manufacturing delays, which can take place for a variety of reasons, from facilities not being available to batch failure occurring. On a positive note, adoption of different production routes could result in shorter production cycles and increased manufacturing output. A series of simulations were carried out in which the dose levels and the manufacturing times were varied, while keeping all other inputs constant. The effect of these changes on the NPV was recorded.

Drug pricing and market share: The drug price and the patient population captured are each crucial to achieving high revenue and for the recovery of investments and to returning a profit. Government regulations and restrictions limit a company's ability to set the price for a new drug (Nicholson & Latham, 1994) and the presence of competitors means that a company needs a strong marketing strategy so as to capture a significant patient population and in order to make profits. Launching a new drug into the marketplace with the goal of achieving maximum penetration and exposure is an expensive advertising and public relations effort (Stonebraker, 2002). Therefore, in the next case study, the drug price and the market share were varied to record the change in the portfolio NPV.

3.1.3. In-house versus contract manufacturing

The sensitivity analysis was used to identify the key uncertainties. The major technical and market uncertainties were incorporated into the final case study presented in this paper. This case illustrates the application of the tool to aid in decision-making in biopharmaceutical development under uncertainty.

This example was based on a biopharmaceutical company with a pipeline of antibody candidates. The company was considering whether to risk building a facility for the commercial manufacture of the antibodies and if so, when, or whether to rely on a contract manufacturer throughout. The use of contract manufacturing organisations (CMOs) for the delivery of material ranging from just process development work to full manufacture of material is a key feature of the biopharmaceutical industry (Byrom, 2000). The options in terms of outsourcing manufacture or building capacity for in-house manufacture must be weighed carefully and will in all events be constrained by the resources available. The decision to build a facility that complies with current good manufacturing practice (cGMP) standards takes considerable time and cost and risks having a facility lying idle if products fail at clinical trials (Langer, 2004). Opting for a contract manufacturer offers potential timesavings, which can be critical to a drug's market share and success. However, contract

Table 4
Parameters that were assigned with probability distributions

Build early option	CMO option	Build late option
Building cost	Delays in contract negotiation	Building cost
Building completion time	Delays in material delivery	Building completion time
Price per treatment	Price per treatment	Price per treatment
Patient population	Patient population	Patient population

manufacturers are expensive and the company will have to relinquish control over the manufacture of material. The software tool was used to model and analyse the different options that were available for manufacturing of material for clinical trials and eventual sales.

The three options considered were:

1. *Build early option (aggressive):* Use the plant facility for the production of material for the clinical trials and start building a new plant at the end of Phase II clinical trials. In this case the manufacturing plant will be ready to supply product(s) to the market upon approval. This is an aggressive and risky strategy.
2. *Contract manufacturing option (cautious):* Contract out the production of material for the clinical trials and the market fully to a CMO and not build at all. This is a cautious strategy, but does mean the company has less control over manufacture.
3. *Build late option (conservative):* The material for the clinical trials is produced within the existing plant and a new facility is built once the first product successfully completes Phase III clinical trials. This would enable the company to start producing its first approved drug in-house by the third year into the market. While the facility for commercial production is being built, a contract manufacturer is used for the first approved drug. It is a cautious strategy but one which results in more company control of manufacturing.

Several assumptions were made for the case study (summarised in Tables 4–8). These assumptions were validated

Table 5
Values and probability distributions for the input parameters

Parameter	Value; probability
Negotiation time	3 months; 50% 6 months; 30% 12 months; 20%
Delays in material delivery (CMO)	0 months; 60% 3 months; 30% 6 months; 10%
Price per treatment	Base case estimation; 50% 80% * Base case estimation; 30% 120% * Base case estimation; 20%
Patient population	Base case estimation; 50% 60% * Base case estimation; 30% 110% * Base case estimation; 20%

Table 6
Phase transition probabilities for each phase (Reichert, 2001)

Monoclonal antibody	Phase 1–2 (%)	Phase 2–3 (%)	Phase 3 to review (%)	Review to approval (%)
Chimeric	86	40	80	100
Humanized	84	72	75	100

Table 7
Probabilities of failure due to technical reasons

	Probability of failure due to technical reasons
Without a CMO	0.30
With a CMO	0.10

Table 8
Key case study assumptions

Assumption	Value
Number of drugs within the portfolio	3
Cost of manufacturing in-house	US\$ 1500 per g
Cost of contracting out	US\$ 2700 per g
Duration of in-house manufacturing	12–24 months
Duration of contract manufacturing	6–18 months

through discussion with industrial experts. The drug-specific attributes for the three antibodies were based on historical data for commercial antibodies (Foo et al., 2001; Farid, 2001). It was assumed that whenever the manufacture of clinical trial material was outsourced, some of the research and development work was handled by the same contract manufacturing company. Drugs that completed the development work successfully then proceeded to the market where a set sales profile was applied. A probability distribution was applied to the parameters subject to uncertainty (Table 4).

The probability distribution for the price per treatment and the patient population was the same for all three options. The building completion time was assigned with a 10% probability of a 1-year delay. The building estimated at US\$ 200 million (Langer, 2004) was expected to be able to produce three monoclonal antibodies at 200 kg/year under cGMP conditions. The cost was given a maximum value of US\$ 250 million (30%) and a lower value of US\$ 180 million (10%).

The phase transition probabilities for the MABs were kept the same for all three options. However, the probability of failure due to technical reasons was assumed to change depending on the option selected. When a CMO was involved the probability of a drug failing due to technical reasons was assumed to be low reflecting the fact that there is experience and knowledge available to the company from the CMO regarding process and product development.

The cost and time data regarding the manufacturing of material through a CMO (Table 8) were compiled after discussions with industrialists and literature (Nicholson & Latham, 1994).

3.2. Results and discussion

3.2.1. Base case results

The first set of results was generated to assess the cost and time of developing a set of drugs given a set level of resources. The costs and time values shown in Fig. 2 are for developing a portfolio of three monoclonal antibodies without uncertainty or risk incorporated. The total cost to develop one drug was calculated by the model to be US\$ 304 million (2002 US\$). DiMasi et al. (2003) concluded in a detailed study concluded that the cost of producing a drug to be US\$ 404 million (2000 US\$). However, DiMasi et al. (2003) used mainly chemical entities for their study. Therefore, a direct comparison is not possible. Fig. 2b shows the time taken for the development process. The longest phase is the third phase as it has the longest clinical trials involving over 3000 patients. The cost and time values depend on the type of drug and therapeutic area.

A common problem encountered by companies is how to deploy staff to ensure projects are completed on time. Fig. 3 shows how the overall demand on personnel increase with the size of the portfolio but also indicate points of low activity and high demands. Being able to predict bottlenecks and poor use of human resources on the basis of simulation results allows companies to plan ahead and to anticipate how business decisions will impact at this level.

3.2.2. Sensitivity analysis

The sensitivity analysis results depicted in Fig. 4 indicate that the critical driver of the portfolio NPV is the size of the market captured. This is then followed by the price set for

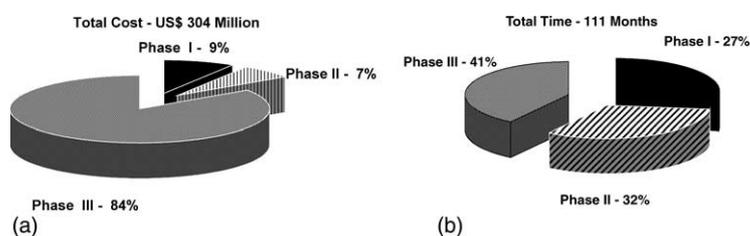


Fig. 2. Breakdown of (a) the cost and (b) the duration of development of one drug. The Phase III stage is the costliest and the longest as it has the largest clinical trials, which involve several thousand patients to prove the efficacy of the new drug.

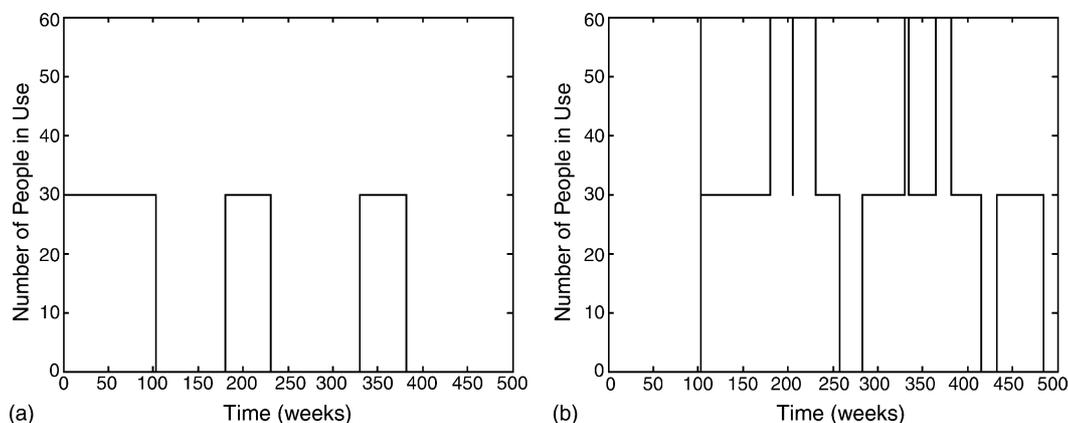


Fig. 3. Utilisation of process development staff for (a) 1 drug and (b) 3 drugs within the portfolio. When a higher number of drugs are in the portfolio, the durations where all the personnel are being used can be noted and used to avoid bottlenecks.

the drug. Stonebraker (2002), in assessing the value of a new drug candidate, concluded that the peak product share and the price per treatment were the most sensitive parameters in determining the NPV.

As the time to market is directly influenced by the time the drugs spends in process development and clinical trials, these two become the next most sensitive factors in drug development. The faster the drug gets into the market, the more time it has to generate revenue before a competitor or a generic drug is introduced.

The number of personnel available for development work acts as a constraint, holding back the drug until the number of personnel required is available for the development work to be done. Therefore, the number of people affects the time to market value directly and is a key driver of the portfolio NPV. The number of personnel needed for manufacturing and clinical trials were not modelled as constraining factors, and therefore they do not appear in the Tornado diagram. The manufacturing tasks were modelled with the availability of the facility as a constraint and the clinical trial were always

outsourced to a contract research organisation as is frequently the case in the industry today.

Delays in building new facilities, delays in the negotiation time and the presence of a competitor all have a negative effect on the NPV. Dose levels (product demand) and the yields do not appear to be a major factor influencing the NPV of the portfolio. Therefore, small increases in the quantities that need to be produced do not affect the NPV. The relatively low cost and duration of manufacturing tasks compared to development work and clinical trials can be cited as a possible reason for this. The probabilities of failure due to technical reasons and at clinical trials are influential factors, but have not been included as their effects are more intuitive. The higher the chance of failure, the more detrimental the effect on the portfolio NPV.

3.2.3. Scenario analysis

The results of the different scenario analyses detailed earlier are presented in contour plots, Figs. 5–7, which explore key decisions in biopharmaceutical development.

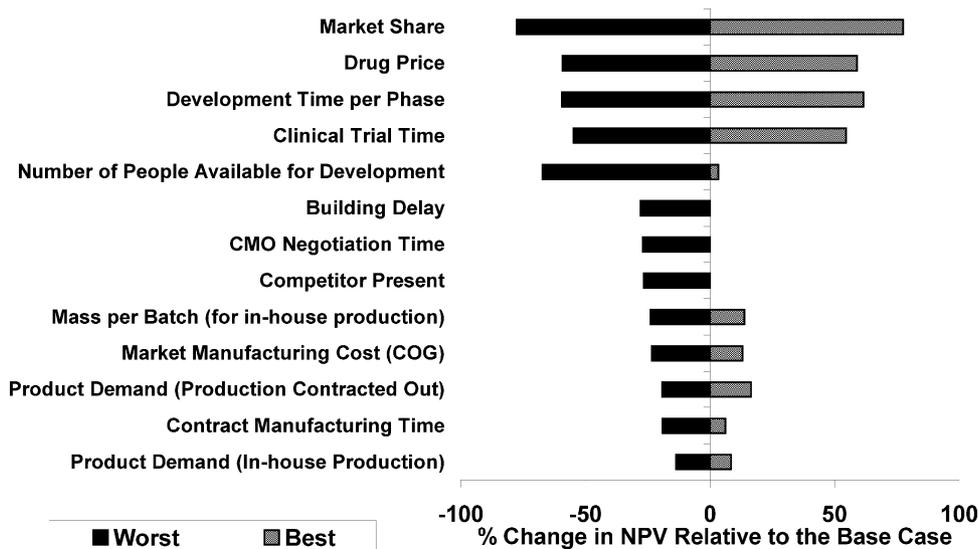


Fig. 4. Tornado diagram showing the sensitivity of the portfolio NPV to input parameters. The vertical axis intersects the horizontal axis at the base case value.

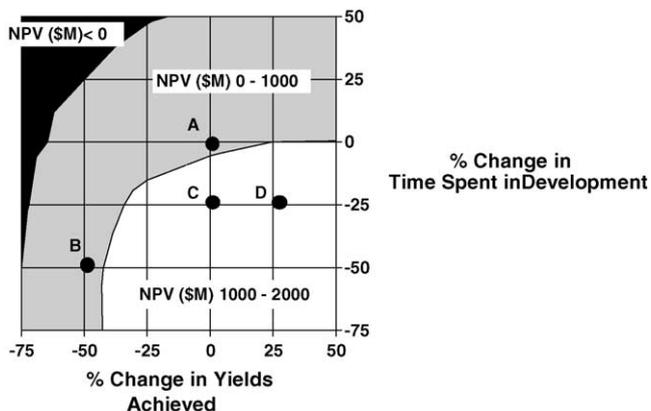


Fig. 5. Portfolio NPV for variations in process development time and yields achieved.

Process efficiency and time spent in development: Fig. 5 illustrates the impact of variations in process development time and yields on the portfolio NPV. The point A marks the base case result. If the desired yields are not achieved by the anticipated deadlines or take longer to achieve, operation moves to the top left hand region of the figure and the NPV will eventually take negative values.

Point B achieves the same NPV as A, but requires a less efficient process and hence less time spent in development. The extra time gained by moving to point B can be used for a different task. By moving to point C or D, the NPV could be increased. In this case, the trade-off is between spending less time in development, resulting in either no efficiency gain (C) or an improved process (D). Point D gives the greatest improvement in NPV of the options.

This level of insight into resource usage is not obvious at first, but very much an asset to decision-making when allocating resources and planning for development programs.

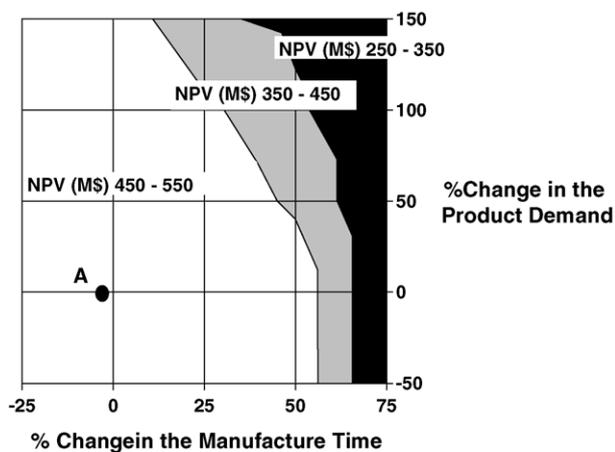


Fig. 6. Portfolio NPV for the variation in the product demand and manufacturing time.

The process development group can use this type of output from the tool to keep a check on the yields and the deadlines necessary to achieve them. If the management feels that the process development team is falling behind, they can take steps to allocate extra resources in order to keep to the schedules or implement other actions to redress the situation. This type of study can be used to quantify the value of spending time in improving process efficiency and trade this against any resulting reduction in time to market for the drug.

Manufacturing time and dose fluctuations: The NPV of the portfolio is not highly sensitive to the manufacturing time and the quantity of material as shown earlier in the Tornado diagram (Fig. 4). Changes in NPV to variations in both the quantity of material that has to be produced as well as changes in manufacturing times are plotted in Fig. 6. Point A refers to the base case value. If the manufacturing time increases beyond 50% of the base case value (2 months campaign time), the portfolio NPV becomes quite sensitive to the manufactur-

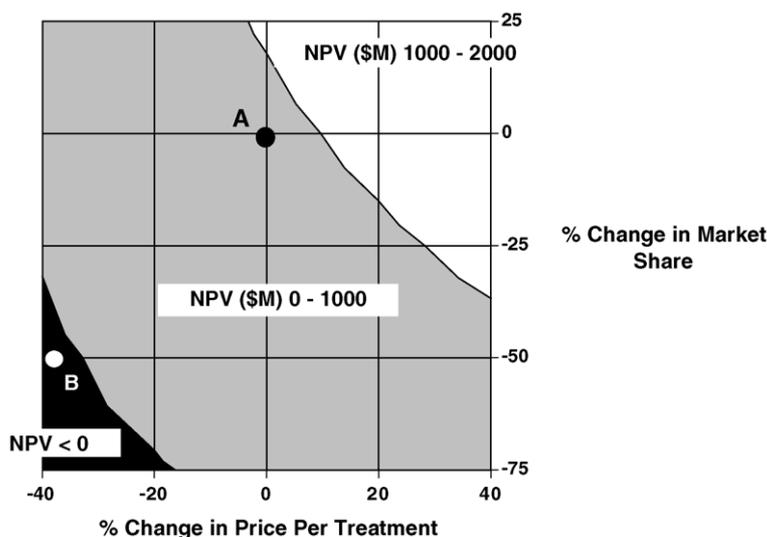


Fig. 7. Portfolio NPV for the variation of the patient population and the price per treatment of the drug candidate.

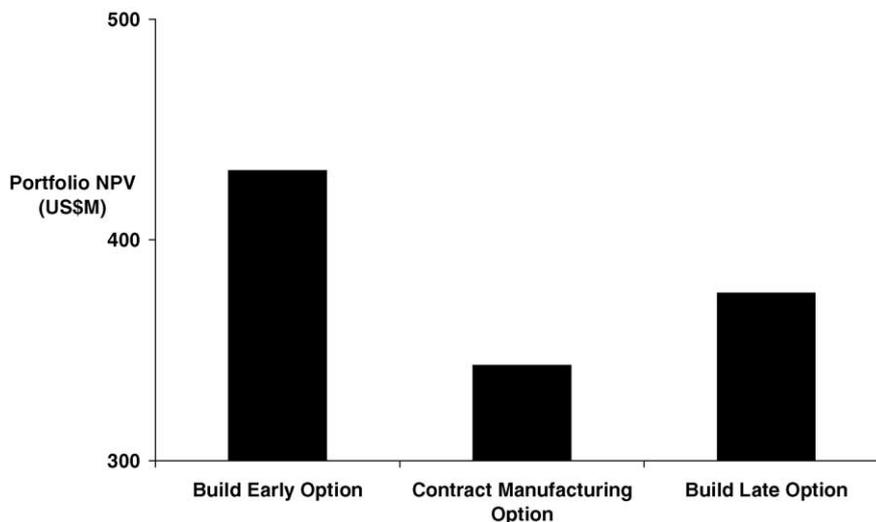


Fig. 8. The portfolio NPV for the three options without the uncertainty and risk incorporated is plotted.

ing time and drops of up to US\$ 100 million can be observed. These results would enable the management to feel confident about pursuing development work on a new drug candidate, which might have high uncertainty in the dose levels and plan for additional manufacturing capacity if required.

Drug pricing and market share: The results of changing the price of the drug and the market share on the portfolio NPV are shown in Fig. 7. As the process of drug development is driven by the profits achieved in the market, it is important to gauge the effects of such fluctuations. The portfolio consisted of a set of breakthrough drugs (A). Lower market capture and an inability to command a high price could shift the portfolio NPV to point B, resulting in a negative NPV. The above results could be used to plan the sales strategy and make judgement on which markets to launch the drug. If the company feels that there is too much competition or the drug is too expensive to get approval from the authorities, using this type of scenario analysis the project could be terminated at an early stage or be held back.

3.2.4. In-house versus contract manufacturing

In the second part of the case study, three options for the manufacturing strategy were explored. Fig. 8 shows the results of the deterministic study that do not account for drug failures. The tool predicted that the option to build early, at the end of Phase II clinical trials, is the most attractive followed by the option to build after the product makes it to the market. The lower portfolio NPV associated with the build late option can be attributed to the high contract manufacturing costs in the first 3 years on the market and the high marketing costs involved in launching the product, which combine to lower the profits made. However, the build late option is still marginally better than the contract manufacturing option (by 10%) due to the savings made by manufacturing in-house during development and once the commercial facility is built.

The outputs generated by the Monte Carlo simulation technique are shown in Fig. 9. Factoring in risk and the uncertainty reduces all the expected NPVs (Fig. 9) relative to the deterministic value (Fig. 8) due to the fact that many drugs fail

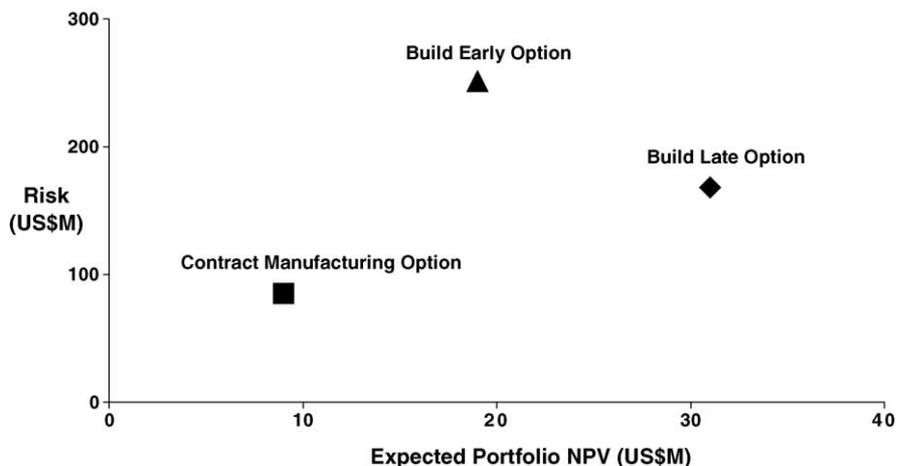


Fig. 9. The reward and risk associated with the three options, after the uncertainty and the risk involved have been factored in.

in clinical trials or for technical reasons. The option with the highest NPV and the lowest risk is preferred. The best option in terms of reward (expected NPV) is the build late option, which is building after at least one drug gets into market. However, the best option in terms of minimising risk is the contract manufacturing option.

Considering all three options, the expected NPV values are within \pm US\$ 20 million of each other and yet the risk values are between \pm US\$ 85 million and \pm US\$ 251 million. Therefore, the decision is most likely to be based on the risk involved with each option. The option of using a contract manufacturer is the least risky as there are no high investments in new facilities to be recovered. Also, the contribution from the CMO in terms of knowledge and experience serves to lower the risk of failure due to technical reasons. The risks in this option, for example delays in negotiation and material delivery, do not appear to have a major effect.

The option of using a contract manufacturer is a cautious strategy. However, if the management is willing to tolerate a higher risk in order to get a higher expected portfolio NPV, the best option would be the build late option. While the risk is minimised by setting the minimum requirement of at least one drug into the market before building, the revenue increases relative to the contract manufacturing option, as it has control over the manufacturing of material after the first 3 years. The risk is still high as the revenue from just one drug is insufficient to recover the full investment on the facility. If the success of two drugs is set as the minimum requirement for starting to build, the risk involved with the option of building after the product gets into the market will be much lower. This decision is further justified by the fact that even if only one drug makes it to the market from this portfolio, other new drug candidates, which might follow (and have not been considered in this case study) could be produced in the same facility.

Accounting for failures and uncertainties knocks the build early option out of first place, highlighting the limitations of relying solely on deterministic results. The option of building early is the second best in terms of reward but has the highest risk. This is because in the case of none of the drugs making it to the market, the company is saddled with a high investment that cannot be recovered. However, when two or all three drugs do make it to the market, the profits are substantial.

4. Conclusions

The development of a prototype application to help decision-making has been presented. It provides a framework to assist decision-making during the development of biopharmaceuticals. The modelling of the drug development tasks provides a transparent process that can be used to manage effectively the allocation of resources and quantify the risks and uncertainties. A comprehensive sensitivity analysis has been carried to identify the important parameters in drug development. The tool has then been used to simulate and analyse

different options and scenarios for development work, clinical trials and the market performance of drugs. The contour plots provide ability to plan for a range of contingencies including uncertainties in manufacturing efficiencies, product demand and the market share captured.

A case study has been used to demonstrate the functionality of the tool to output the expected NPV of a small drug portfolio under uncertainty for different manufacturing options. The effects of technical and market uncertainties on the question of whether to build or use a contract manufacturer were analysed using the Monte Carlo simulation. The simulation studies highlighted the benefits of incorporating uncertainties when ranking different strategies. Effective use of the simulation outcomes can lead to risk mitigation, more effective use of resources and improved overall economic performance. Future work will concentrate on enhancing the decision-support capabilities within the tool to select drugs for portfolios where risks and costs are balanced.

Acknowledgements

This work is part of an Innovative Manufacturing Initiative (IMI) project titled “Integrating Business and Process Needs in the Successful Commercialisation of Biopharmaceuticals” funded by the Engineering and Physical Sciences Research Council, UK. The funding for Anuradha Rajapakse from the Overseas Research Students Awards Scheme is gratefully acknowledged. The Advanced Centre for Biochemical Engineering at UCL houses the Innovative Manufacturing Research Centre (IMRC) and collaborates with a range of academic partners and biopharmaceutical and biotechnology companies.

References

- Byrom, D. (2000). Role and timing of process development for biopharmaceutical manufacture. *Pharmaceutical Technology Europe*, 12(3), 52–56.
- DiMasi, J. A., Hansen, R. W., & Grabowski, H. G. (2003). The price of innovation: New estimates of drug development costs. *Journal of Health Economics*, 22, 151–185.
- Farid, S. (2001). A decision-support tool for simulating the process and business perspectives of biopharmaceutical manufacture, University College London, *Ph.D. Thesis*.
- Farid, S., Novais, J. L., Washbrook, J., & Titchener-Hooker, N. J. (2000). A tool for modelling strategic decisions in cell culture manufacturing. *Biotechnology Progress*, 16, 829–836.
- Farid, S., Washbrook, J., & Titchener-Hooker, N. J. (2001). Decision-support tool for risk analysis in biopharmaceutical manufacture. In D. Dochain & M. Perrier (Eds.), *Eighth International Conference on Computer Applications in Biotechnology (CAB8): Modelling and Control of Biotechnological Processes* (pp. 167–171).
- Foo, F., Karri, S., Davies, E., Titchener-Hooker, N., & Dunnill, P. (2001). Biopharmaceutical process development. Part I. Information from the first product generation. *Biopharm Europe*, 58–64.
- Gatica, G., Papageorgiou, L. G., & Shah, N. (2003). Capacity planning under uncertainty for the pharmaceutical industry. *Transactions of IChemE*, 81 (A), 665–667.

- Ginsberg, P.L., Bhatia, S., & McMinn, R.L. (2002). *The Road Ahead for Biologics Manufacturing*, U.S. Bancorp Piper Jaffray Equity Research, NY, <http://www.piperjaffray.com> (accessed 2003).
- Jain, V., & Grossmann, I. E. (1999). Resource-constrained scheduling of tests in new product development. *Industrial and Engineering Chemistry Research*, 38, 3013–3026.
- Karri, S., Davies, E., Titchener-Hooker, N. J., & Washbrook, J. (2001). Biopharmaceutical process development. Part III. A framework to assist decision making. *Biopharm Europe*, 76–82.
- Keelin, T., Shew, B. (2003). *Third Generation Portfolio Management*. Strategic Decisions Group Publication.
- Langer, E. S. (2004). Manufacturing capacity put on simmer. *Bioprocess International*, 22–28.
- Levis, A. A., & Papageorgiou, L. G. (2004). A hierarchical solution approach for multi-site capacity planning under uncertainty in the pharmaceutical industry. *Computers and Chemical Engineering*, 28, 707–725.
- Lim, A. C., Washbrook, J., Titchener-Hooker, N. J., & Farid, S. (2004). A decisional-support tool to model the impact of regulatory compliance activities in the biomanufacturing industry. *Computers and Chemical Engineering*, 28(5), 727–735.
- Luehrman, T. A. (1994). Financial engineering at Merck. *Harvard Business Review*, 94–97.
- Mustafa, M. A., Washbrook, J., Lim, A. C., Zhou, Y., Titchener-Hooker, N. J., Morton, P., Berezenko, S., & Farid, S. S. (2004). A software tool to assist business-process decision-making in the biopharmaceutical industry. *Biotechnology Progress*, 20(4), 1096–1102.
- Nicholson, I., & Latham, P. (1994). When make or buy means make or break. *BioTechnology*, 12, 473–477.
- Reichert, J. M. (2001). Monoclonal antibodies in the clinic. *Nature Biotechnology*, 19.
- Rogers, M. J., Gupta, A., & Maranas, C. D. (2002). Real options based analysis of optimal pharmaceutical research and development portfolios. *Industrial and Engineering Chemistry Research*, 41, 6607–6620.
- Soegaard, M. (2003). Maximising return on investment with R&D portfolio management. *European Biopharmaceutical Review*, 12–15.
- Stonebraker, J. S. (2002). How Bayer makes decisions to develop new drugs. *Interfaces*, 32(6), 77–90.
- Subramanian, D., Pekny, J. F., & Reklaitis, G. V. (2000). A simulation-optimisation framework for addressing combinatorial and stochastic aspects of an R&D pipeline management problem. *Computers and Chemical Engineering*, 24, 1005–1011.