Dynamic Optimisation of the Drug Development Pathway
Anuradha Rajapakse, Nigel John Titchener-Hooker, Suzanne Farid*
The Advanced Centre for Biochemical Engineering
Department of Biochemical Engineering, University College London,
Torrington Place, London WC1E 7JE, UK.

Abstract
Current pressures of cost and speed to market are driving the need for more effective means of assessing the value and risks of drug portfolios. This paper presents research to generate a prototype computer-aided 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 the question of outsourcing vs. in-house manufacture of material for clinical trials.

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

1. Introduction

Given the time, cost and risk associated with drug development, biopharmaceutical companies typically need to have a portfolio of drugs in the pipeline if they are to remain successful. Current pressures of cost and speed to market in the biopharmaceutical industry are 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, 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).

However managing an R&D portfolio is complicated by constraints on budget, the levels of human resources and the available capacity and how best to deploy them. 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

* Author to whom correspondence should be addressed: s.farid@ucl.ac.uk
of competition. Given these factors the survival of a company can depend on the key decisions made during the development of each drug within a portfolio. 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 *et al.*, 2001). The use of a prototype decision-support tool for controlling the cost of goods in biopharmaceutical manufacture under uncertainty has been demonstrated (Farid *et al.*, 2001; Lim *et al.*, 2003). 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 developed to predict the outcomes of employing different development strategies for a portfolio of biopharmaceutical drugs proceeding through the development pathway.

2. Design Methodology

2.1. Modelling approach

A structured model of the biopharmaceutical pathway was used in order to achieve rapid modelling of the impact of business decisions made during the management of biopharmaceutical product development. The conceptual framework 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 (Figure 1). As depicted in Figure 1, the pathway includes development, manufacture, clinical trials and the drug’s performance in the market. The hierarchical structure enables the user to prototype a management strategy at the required level of detail and perform a series of ‘what–if scenarios’ rapidly.
It also allows the user to access a breakdown of the outputs. Therefore the costs and durations of specific tasks (e.g. cost and duration of clinical trials of Phase 1) are available for analysis or comparison.

2.2. Implementation
For the design, implementation and application of the tool, data for a portfolio of monoclonal antibodies progressing from Phase 1 development through to the market was used. The model simulates a time period of twenty 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). 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). Specific blocks to simulate the above 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). 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 and a database built at UCL (Foo et al, 2001). 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 for example include deciding priorities for drug development or deciding which, if any drug would be made available to be contracted out for manufacture. The default strategy was to minimise the waiting time in development. Hence for example if the company facility is occupied the model will opt to contract out the production of the next drug awaiting manufacture for clinical trials provided adequate capital is available. The risks involved in the process of drug development were incorporated into the model (Di Masi et al, 1991). Technical uncertainties included the risk of failure at the end of each phase of clinical testing. The analysis uses Monte Carlo simulation to imitate the random failure of drugs and the market uncertainties, which include the volatility in the forecasted demands and the likely selling price of the drugs.

The outputs of the model include the costs of developing the drug portfolios and the time to market. The cost analysis was extended to include other profitability indicators such as the Net Present Value (NPV). NPV calculates the current value of a future cash flow and is a very useful metric for the comparison of current costs to undertake a project versus the potential benefits, in this case revenues, that the project will yield sometime in the future. Consequently, using this tool the users can perform strategic, tactical and operational analysis according to their particular goals.
3. Case Study

3.1. Set-up

To evaluate the functionalities of the software tool, the progress of three monoclonal antibodies from discovery to the market was simulated. This is a necessarily small sample selected so as to provide confidence in the simulation outputs. Given the high capital investment, operating costs and the risks associated with manufacturing material for clinical trials, many pharmaceutical companies, large and small have begun to rely on contract manufacturing organisations (CMOs) for the delivery of material. Outsourcing could range from just manufacturing to doing both the development work and the manufacturing of material. The options in terms of outsourcing or in-house manufacture must be weighed carefully and will in all events be constrained by the resources available.

The software tool was used to model and analyse the different options. At the start of each simulation the manufacturing strategy was set. Each simulation was run with a different drug contracted out for some of the development work and the manufacture of the clinical trials material. Several assumptions were made for the case study (Table 1-3). These assumptions were validated through discussion with industrial experts. The drug specific attributes for the 3 antibodies were based on historical data for commercial antibodies (Foo *et al*., 2001; Farid *et al*., 2001). During the first set of simulations, a 100% success rate was applied. For the second set of simulations the risk of clinical failure was factored in to analyse the effect on the performance of the portfolio. Failure was assumed to occur at the end of a phase. The chance of failure at each phase was derived from Di Masi *et al* (1991) and was kept the same for each drug. The clinical trials were assumed to be contracted out for all the drugs. 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. For simplicity successful drugs were expected have constant sales for the duration of the remaining patent life.

The first simulations were run assuming two different levels of capital were available ($750M and $500M). This was done to study the effect of constraining resources on the portfolio’s performance. Monte Carlo simulations were used to account for the effects of failure with 200 simulations per different strategy being run.

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Description</th>
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<tbody>
<tr>
<td>1</td>
<td>Contract out manufacture of drug 1, which is a low dose, high market drug</td>
</tr>
<tr>
<td>2</td>
<td>Contract out manufacture of drug 2, which is a medium dose, medium market drug</td>
</tr>
<tr>
<td>3</td>
<td>Contract out manufacture of drug 3, which is a high dose, low market drug</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Phase Transition Probability</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase Transition Probability</td>
<td>0.75</td>
<td>0.48</td>
<td>0.635</td>
</tr>
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Table 3. Key case study assumptions.

<table>
<thead>
<tr>
<th>Assumption</th>
<th>Value</th>
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<tbody>
<tr>
<td>Number of drugs in the portfolio</td>
<td>3</td>
</tr>
<tr>
<td>Cost of manufacturing in-house</td>
<td>$500,000 per batch</td>
</tr>
<tr>
<td>Cost of contracting out manufacturing</td>
<td>$1,000,000 per batch</td>
</tr>
<tr>
<td>Duration of in-house manufacturing</td>
<td>12 – 24 months</td>
</tr>
<tr>
<td>Duration of contract manufacturing</td>
<td>6 – 18 months</td>
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3.2. Simulation results and discussion

The results in Figure 2 demonstrate how opting to contract out drug 1 results in the highest NPV because drug 1 requires a longer time in manufacturing. When drug 1 is contract manufactured, company resources are released for more drugs to be brought into the market earlier. As drug number 1 is also a high value drug, bringing it to the market quicker by contract manufacturing it, contributes to a higher NPV. Lowering the capital available to $500 million reduces the NPV of the portfolio because the time to market for drugs 2 and 3 are delayed. The development of these drugs is held back till drug 1 generates enough revenue for reinvestment in the pipeline.

Figure 3 shows the expected NPV and the risk associated with contracting once the chance of clinical failure is included. In all cases the risk (expressed as $M) is very high and similar reflecting the nature of development. The analysis highlights that although outsourcing drug 1 is still the optimal option, the expected NPV values are more than 80% lower than the deterministic NPV values shown in Figure 2. This highlights the importance of including failure. The dynamic relationship between the management strategy of the drug candidates and the portfolio NPV has been shown using a simple case study. Such results and analysis enable the management to view the possible manufacturing options in a meaningful way and to deploy resources appropriately.

![Figure 2. NPV values for outsourcing drug 1, 2 or 3 with a capital budget of $750 million and $500 million without the chance of failure.](image-url)
Figure 3. Expected NPV and the risk involved with the three outsourcing options.

4. Conclusions

The development of a prototype application has been presented. It provides a framework to manage the development of biopharmaceuticals. A case study has been used to demonstrate the functionality of the tool to output the net present value (NPV) of a small drug portfolio under different contracting out options. Future work will concentrate on enhancing the optimisation capabilities within the model. The tool will be used to simulate and analyse the dynamic relationship between all the drugs and its effect on the portfolio as a whole as they proceed through the development process.

References


