COST EVALUATION AND PORTFOLIO MANAGEMENT OPTIMIZATION FOR BIOPHARMACEUTICAL PRODUCT DEVELOPMENT

Wenhao Nie

The Advanced Centre for Biochemical Engineering
Department of Biochemical Engineering
UCL

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I, Wenhao Nie, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

ABSTRACT

The pharmaceutical industry is suffering from declining R&D productivity and yet biopharmaceutical firms have been attracting increasing venture capital investment. Effective R&D portfolio management can deliver above average returns under increasing costs of drug development and the high risk of clinical trial failure. This points to the need for advanced decisional tools that facilitate decision-making in R&D portfolio management by efficiently identifying optimal solutions while accounting for resource constraints such as budgets and uncertainties such as attrition rates. This thesis presents the development of such tools and their application to typical industrial portfolio management scenarios.

A drug development lifecycle cost model was designed to simulate the clinical and non-clinical activities in the drug development process from the pre-clinical stage through to market approval. The model was formulated using activity-based object-oriented programming that allows the activity-specific information to be collected and summarized. The model provides the decision-maker with the ability to forecast future cash flows and their distribution across clinical trial, manufacturing, and process development activities. The evaluation model was applied to case studies to analyse the non-clinical budgets needed at each phase of development for process development and manufacturing to ensure a market success each year. These cost benchmarking case studies focused on distinct product categories, namely pharmaceutical, biopharmaceutical, and cell therapy products, under different attrition rates.

A stochastic optimization tool was built that extended the drug development lifecycle cost evaluation model and linked it to combinatorial optimization algorithms to support biopharmaceutical portfolio management decision-making. The tool made use of the Monte Carlo simulation technique to capture the impact of uncertainties inherent in the drug development process. Dynamic simulation mechanisms were designed to model the progression of activities and allocation of resources. A bespoke multi-objective

evolutionary algorithm was developed to locate optimal portfolio management solutions from a large decision space of possible permutations. The functionality of the tool was demonstrated using case studies with various budget and capacity constraints. Analysis of the optimization results highlighted the cash flow breakdowns across both activity categories and development stages.

This work contributed to the effort of providing quantitative support to portfolio management decision-making and illustrated the benefits of combining cost evaluation with portfolio optimization to enhance process understanding and achieve better performance.

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ABBREVIATIONS

API	Active pharmaceutical ingredient
CAPM	Capital asset pricing model
CMO	Contract manufacturing organization
COG	Cost of goods
DCF	Discounted cash flow
FDA	Food and Drug Administration
FTE	Full-time equivalent
GMP	Good manufacturing practice
IBEA	Indicator-based evolutionary algorithm
IND	Investigational New Drug
IRR	Internal rate of return
LOA	Likelihood of approval
mAb	Monoclonal antibody
MOEA	Multi-objective evolutionary algorithm
MILP	Mixed-integer linear programming
NDA/BLA	New Drug Application/Biological License Application
NPV	Net present value
NSGA-II	Non-dominated sorting genetic algorithm-II
QC/QA	Quality control/quality assurance
R&D	Research and development
TP	Transition probability

CHAPTER 1

LITERATURE REVIEW

1.1 INTRODUCTION

The biopharmaceutical R&D activities are highly costly, time consuming and technology intensive. Each biopharmaceutical new drug development process costs more than $1.2 billion (DiMasi & Grabowski 2007), with the development duration between the new drug discovery and market approval ranging from 5 to 10 years (Werner 2004). The development of a biopharmaceutical new drug consists of several distinct phases, which require specific planning of resource investment. The manufacture of biopharmaceuticals is one of the most highly regulated and complex processes that requires intensive control and significant capital investment on the design, planning and construction of the facility (Goldstein & Thomas 2004). Drug developers are also facing diminishing returns from R&D investment as the number of new products approved by FDA per billion dollar on R&D spending has halved every 9 years (Scannell et al. 2012). To maintain competitive advantages, biopharmaceutical developers must sustain intensive innovation either from in-house pipeline development or by acquiring outside product candidates. This brings up the need of a comprehensive decision-support tool for drug developers that not only focuses on finding the optimal portfolio management solutions, but also provides guidance on budget and capacity planning. Therefore, in this thesis, computational decisional tools were developed to optimize the biopharmaceutical portfolio decision-making under resource constraints and to characterize the costs associated with various development activities.

In this chapter, the background and scope of this work are introduced by reviewing published literature on the drug development process, biopharmaceutical portfolio management decision-making, and modeling & optimization approaches. The remainder of this chapter is structured as follows. Section 1.2 introduces the biopharmaceutical drug development

process, including a brief overview of the activities and stages that constitute the drug development lifecycle. Section 1.3 reviews some of the key topics that influence biopharmaceutical portfolio management decision-making. Important computational modeling and optimization techniques are discussed in Section 1.4 as well as their implementations in biopharmaceutical industry. Finally, the aim and organization of this thesis are presented in Section 1.5.

1.2 BIOPHARMACEUTICAL DRUG DEVELOPMENT PROCESS

Biopharmaceuticals have been defined as "protein or nucleic acid based pharmaceutical substances used for therapeutic or *in vivo* diagnostic purposes, which are produced by means other than direct extraction from natural biological sources" (Walsh 2006). The biopharmaceutical drug development process consists of a number of different stages. In the pre-clinical trial phase, the new drug candidate is subject to a range of tests both *in vitro* and in animals in order to characterize the drug in terms of its likely safety and effectiveness in treating its target disease. Upon completion of the pre-clinical trial, the drug developer applies to regulatory authorities (e.g. the FDA in USA) for approval to commence clinical trials in humans, which are required to prove that the drug is safe and effective when administered to patients. The clinical trial work commences once the toxicity of the drug has been characterized, and the company normally patents the drug in order to ensure a period of monopoly in the market.

Conventionally, there are three major phases of human clinical trials before a drug can be granted market approval: Phase I mainly focuses on the safety aspect of the product and the size of the trial is relatively small compared to other clinical trial phases. In Phase II, the efficacy of the drug is put to test where double-blinded studies are normally adopted to ensure objectivity. This is also the phase with the highest probability of failure for biopharmaceuticals. Large numbers of patients are required in Phase III trials as the regulatory authorities expect more accurate estimates of the efficacy and dosage of the drug in a larger population before granting

permission for marketing. This is also the most expensive and lengthy phase for development of biopharmaceuticals. Preparations for market launch are also triggered at this phase, since the manufacturing process is normally locked from this stage onwards.

At the regulatory review stage, the drug developer is required to gather all pre-clinical and clinical data, along with characterization of the production process, and submit them to the regulatory authorities for approval of market entry. The go-ahead from regulatory authorities after the review stage enables the drug developer to legally manufacture and market the product for profit. But regulatory involvement does not end at this point; post-marketing surveillance, also known as Phase IV clinical trial, is generally undertaken, in which the company is obliged to report any subsequent drug-induced side effects or adverse reactions. Regulatory authorities also inspect the manufacturing facilities every two years to ensure that satisfactory manufacturing standards are complied (Walsh & Murphy 1999).

1.2.1 Development time, cost, and success rate

Biopharmaceutical drug development is a lengthy and expensive procedure. DiMasi claimed that the estimated average out-of-pocket clinical period cost per approved new drug is $361 million, and the average out-of-pocket pre-clinical period cost per approved new drug is $198 million (DiMasi & Grabowski 2007). These results are concluded by evaluating project-level aggregated annual expenditure data from biotech firms, and are primarily targeted on therapeutic recombinant proteins and monoclonal antibodies (mAb). The risks associated with the new drug development process are incorporated to derive these figures.

There are four main factors that drives the drug R&D costs: 1) the out-of-pocket costs for development phases, 2) the success rates, 3) the development times, and 4) the cost of capital (Jorge Mestre-Ferrandiz 2012). Several published empirical studies have summarized the out-of-pocket costs of different clinical phases from databases of pharmaceutical companies. Table 1.1 presents the predominate figures in pharmaceutical

and biopharmaceutical product development cost estimations. There are significant variations in the out-of-pocket phase costs of almost all phases of drug development process among the studies. For clinical trial Phase I to III, Bogdan and Villiger's (2010) estimations of the out-of-pocket costs are considerably lower than other sources.

Table 1.1 Published out-of-pocket phase costs for developing pharmaceuticals and biopharmaceuticals

Source	Product category	Pre-clinical ($million)	Phase I ($million)	Phase II ($million)	Phase III ($million)	Review (%)
(DiMasi et al. 2003)	Pharmaceutical	N/A	15.2	23.5	86.3	N/A
(DiMasi & Grabowski 2007)	Biopharmaceutical	59.88[a]	32.28	37.69	96.09	
(Adams & Brantner 2006)	Pharmaceutical	N/A	32	40	113	
(Bogdan & Villiger 2010)	Biopharmaceutical	3~7	4~5	10~11	30~60	3[b]
(Paul et al. 2010)	Pharmaceutical	5	15	40	150	40

[a] Pre-clinical cost obtained by multiplying the estimated clinical phase cost per investigational molecule by a ratio of pre-clinical to clinical expenditures.

[b] The cost of submission in the US and Europe.

In 2003, DiMasi and co-workers estimated that the total development cost per drug was $802 million (DiMasi et al. 2003). This was considered to be lower than the real situation by Adams and Brantner, who estimated that the average capitalized development cost per new drug is $1 billion (Adams & Brantner 2006), using the publicly accessible database Pharmaprojects. DiMasi responded with new figures that raised the estimation of capitalized cost to $1.2 billion for biopharmaceuticals (DiMasi & Grabowski 2007). Together, these studies show that the cost of innovation in biopharmaceutical industry is rising.

Adams and Brantner also estimated the durations of clinical trial phases for drugs being developed by different groups of firms by market position. The average durations of clinical trials for three of the highly ranked groups of pharmaceutical firms are presented in Table 1.2.

Table 1.2 Average phase time for investigational compounds by firm (Adams & Brantner 2006).

	Phase duration (months)		
Development stage	Top 10 by 2001 income	Top 20 by *Fortune* rank	Top 10 by drug count
Phase I	17	21	18
Phase II	19	23	27
Phase III	25	29	28

The success rates of monoclonal antibody therapeutics are presented in Table 1.3. These data were collected by the Tufts Centre in a study of drug development, which included 355 mAb therapeutic products in clinical studies sponsored by more than 100 commercial firms worldwide (Reichert 2001). According to the consolidated results, the type of the mAb also has an impact on its clinical trial success rates. As presented Table 1.3, the average success rate of mAb therapeutics is around 20%.

Table 1.3 Success rates for mAb therapeutics by type and application (Reichert 2001).

mAb type and application	Success rate on approval (%)
Oncological chimeric mAb	18
Oncological humanized mAb	24
Immunological chimeric mAb	22
Immunological humanized mAb	19

The success rates of investigational biopharmaceuticals provide drug developers with a picture of the probable outcome of their development projects. However, from a development process modeling point of view, the phase transition probabilities more accurately characterize the likelihood of a product reaching certain development stages. Evaluation of expected and capitalized cost for developing novel biopharmaceuticals is largely dependent on the phase transition probabilities.

Several studies have been published on the phase transition probabilities for pharmaceuticals and biopharmaceuticals in various therapeutic areas, selected results from which are presented in Table 1.4. In the area of monoclonal antibodies, a study conducted by Reichert summarized the phase transition probabilities for mAb in clinical trials from 1980 to 2000 (Reichert 2001); those results were further updated when a follow-on study focusing on mAb therapeutics from 1980 to 2006 was conducted in 2008 (Reichert 2008). Table 1.4 shows the data on humanized mAb from these studies. For biopharmaceuticals and pharmaceuticals in general, the phase transition probabilities were summarized in cost estimation studies, in which the expected capitalized cost for developing one successful product was estimated based on the number of products required in each phase (DiMasi & Grabowski 2007). Additional data came from a study on a database of more than 1055 pharmaceutical drugs, summarizing the probabilities of entering a given phase, which can also be translated into phase transition probabilities displayed in Table 1.4 (Adams & Brantner 2006). The

probabilities of phase transition from pre-clinical trial to Phase I trial for pharmaceuticals was estimated in a study focusing on improving R&D productivity for the pharmaceutical industry (Paul et al. 2010). Finally, the latest study on clinical success rates of drugs in various therapeutic areas summarized the phase transition probabilities for new molecular entities (NMEs) and biologics by FDA classification. The phase transition probabilities of large molecules and mAbs from Biomedtracker product categories were also presented (Hay et al. 2014). These results provide important source of information for further analyses.

Table 1.4 Phase transition probabilities of pharmaceutical and biopharmaceutical clinical trials

Source	Product category	Pre-clinical to Phase I (%)	Phase I to II (%)	Phase II to III (%)	Phase III to review (%)	Review to market (%)
Reichert 2001	Humanized mAbs	N/A	84	72	75	100
Reichert 2008	Humanized mAbs	N/A	83	44	82 (Phase III to approval)	
DiMasi & Grabowski 2007	Pharmaceutical	N/A	71	44.2	68.5 (Phase III to approval)	
	Biopharmaceutical	N/A	83.7	56.3	64.2 (Phase III to approval)	
Paul et al. 2010	Pharmaceutical	69	54	34	70	91
Adams & Brantner 2006	Pharmaceutical	N/A	61	72	43 (Phase III to approval)	
Hay et al. 2014	NMEs	N/A	64.2	28.6	53.2	76.5
	Biologics	N/A	68.4	37.9	63.2	88.8
	Large molecules	N/A	65.8	37.7	60.1	88.6
	mAbs	N/A	70.1	38.1	60.7	86.8

1.2.2 Manufacturing biopharmaceuticals

Biopharmaceutical manufacturing is one of the most highly regulated and complex processes that requires intensive control and capital investment for design, planning and construction of the facility (Goldstein & Thomas 2004). The production process can be divided into upstream and downstream processing. Upstream processing refers to the generation of the product through fermentation or cell culture processes, while downstream processing refers to the purification of the product from the fermentation broth and the formulation of the final product. The bulk of biopharmaceuticals currently on the market are mainly produced by genetic engineering using various recombinant expression systems. Although a wide range of potential protein production systems are available, most of the recombinant proteins that have gained market approval so far are produced either in *E.coli* or in mammalian cell lines. Using *E.coli* as a source of biopharmaceutical production has certain advantages such as the high expression rate and rapid growth rate. The vast bulk of proteins synthesized by *E.coli* are intracellular; therefore additional primary processing steps are required to break cells, and purification processes are required to separate target proteins from other impurities. On the other hand, mammalian cell lines as a source of biopharmaceutical production are capable of producing special protein products that require post-translational modifications. However, compared to *E.coli*, mammalian cell lines require more complex nutritional feeding and the growth is relatively slow. Additionally, mammalian cells are often considered more fragile when exposed to shear forces. The disadvantages of both expression systems for biopharmaceutical production increase the complexity of the manufacturing process and production cost.

The number of patients needed for a clinical study dictates the minimum material requirement. Table 1.5 presents details of the typical dosage and patient numbers in clinical trials and in market (Simaria et al. 2012).

Table 1.5 Typical dosage and patient number for clinical trials and market

Material requirement level	Low	Medium	High
Dosage per body weight (mg/kg)	1	7	15
Dosage (mg), 150kg BW	150	1050	2250
No. of doses per patient per year	6	26	52
No. of patients in Phase I	20	40	80
No. of patients in Phase II	100	200	300
No. of patients in Phase III	1000	2000	3000
No. of patients in market	10000	100000	1000000

According to the range of dosage and patient numbers provided in Table 1.5, the possible range of batch numbers required for each phase for the three material requirement levels can be calculated (see Table 1.6). An illustration of the kilogram demands and batch numbers is shown in Table 1.6 for an assumed titre of 3g/L for mAb production for small and large scale and fermenter space efficiency of 70% (Chon & Zarbis-Papastoitsis 2011). . One contingency batch was added for production of each clinical trial stage, as there is risk of contamination (Lim et al. 2005).

Table 1.6 Material and batch required for clinical trial production.

Clinical trial material requirement level	Low	Medium	High
Phase I material (g) per year	18	1092	9360
Phase II material (g) per year	90	5460	35100
Phase III material (g) per year	900	54600	351000
Phase I batch per year (100L)	2	7	46
Phase II batch per year (500L)	2	7	35
Phase III batch per year (5000L)	2	7	35

Note: Titre is assumed at 3g/L level and working volume 70%. One contingency batch added for each clinical trial.

1.3 BIOPHARMACEUTICAL PORTFOLIO MANAGEMENT DECISION-MAKING

Apart from the characteristics of biopharmaceutical products overviewed in the previous section, portfolio management decision-making at an organizational level is also driven by parameters both inside and outside the boundary of organizations. In this section, the single decision-making criterion, net present value (NPV) is introduced, along with a number of factors that influence biopharmaceutical portfolio management decision-making.

Table 1.7 lists the key factors that influence biopharmaceutical portfolio management decision-making. For the decision-makers, these factors can be the resource characteristics of the firm, such as the capacity for production of biopharmaceuticals at commercial scale and the availability of large amounts of R&D budget, or the environment that changes the industrial product development landscape and market potential. The factors within the boundaries of firms can be altered in the decision-making process in order to achieve better outcomes. The factors outside the boundaries of firms can only be treated as given, or inputs to the decision-making process.

Table 1.7 Factors that drive the portfolio management decision-making

Factor	Implications to decision-making
Product market potential	This factor affects the amount of cash inflow once the product is approved for marketing. It has no cash flow implication if the product fails. Therefore the more likely the product goes to market, the more influential this factor becomes.
Capacity bottleneck	This factor could be potentially devastating as it adversely influences the capability of drug development firms realizing the full value of product. Portfolio management decisions should comply with the capacity planning of the firm.
R&D budget	Increasing the R&D expense loosens the restriction on maximum number of projects the drug development firms can take. However, the extra fund could potentially alter the cost-of-capital for the firm, depends on the source of the fund and existing capital structure of the firm.
Industrial landscape on new product development	Key considerations when the environment of new product development changes: Does it introduce more competition? Is there any opportunity to add value by acquiring outside products or out-licensing in-house product?

1.3.1 Net present value

Net present value (NPV) has been widely accepted as the quantitative indicator of the value brought by the investment with implications to future cash flows. The NPV rule for investment decision-making suggests using NPV as the sole criterion and accepting the strategy that maximizes the portfolio NPV. Compared to other investment decision-making criteria, the NPV rule has the following advantages:

1. It can be universally applied to almost all industrial decision-making optimization scenarios that concern the impact on future cash flows.

2. It takes into account the length of investment projects by using the discounted cash flow method.
3. It covers the potential benefit of investment even after the cost of investment is fully recovered. Decision-making criteria based on payback period only focuses on the length it takes the project to recover the cost, but overlook the cash flows generated by the project afterwards. Using the NPV rule, decision alternatives that lead to different cash flow projections after the cost is fully recovered can be distinguished.
4. Compared to the internal rate of return (IRR) rule, the NPV rule has the flexibility of covering the investment projects that may generate mixed positive and negative cash flows. With these projects, a single IRR cannot be used to describe the returns of investment.

However, when applying the NPV rule for investment decision-making, the users do need to specify the appropriate discount rate, which could be difficult to obtain. The concept of discount rate is originated from opportunity cost, which requires that the return of investment should be at least equal to the investment in financial markets that bears the same risk. Failing this, the investment decision will lead to negative NPV. For decision-making at corporate level, the firm's weighted average cost of capital is often used as discount rate.

Empirical studies on cost-of-capital of pharmaceutical and biopharmaceutical industry have shown that using capital asset pricing model (CAPM), the real cost-of-capital ranges from 8.6% to 9.5% for pharmaceutical firms, and 8.6% to 10.3% for biotechnology firms. Using Fama and French model (F-F), the cost-of-capital for pharmaceutical firms ranges from 8% to 9.5%, and for biotechnology firms it ranges from 8.2% to 10.5%, depending on the size of the firm (Harrington 2012).

1.3.2 Construction of industrial manufacturing facilities

For new biopharmaceutical developers who do not suffer from harsh budget constraints, building an in-house manufacturing facility for new product manufacturing is considered more profitable than using contract

manufacturing organizations (CMO) in the long run (Demeter 2003). A previous process simulation and optimization model also suggests that building an in-house facility tends to result in more profit in the future than using CMOs (George et al. 2007).

However, the building of an in-house facility is time-consuming and expensive. A commercial scale biopharmaceutical manufacturing facility normally takes 3 to 4 years to establish, including the design, procurement, construction, process qualification and validation (Thiel 2004). Fixed capital cost for building a biopharmaceutical manufacturing plant capable of producing 50kg therapeutic protein annually is €300 million to €500 million with an up-front €100 million for commissioning (Werner 2004). The capital investment for building a facility with six 15,000L large-scale bioreactors on mAb production is $500 million, and $125 million if using disposables and reduce the scale to 2000L (Kelley 2009). Such costs have to be taken into consideration when making management decisions.

1.3.3 Contract manufacturing

The time factor for R&D of biopharmaceuticals is critical, as developers need to recover their investment by pushing products to market. Because of the lengthy construction time for building a commercial manufacturing facility, drug developers have to plan the fixed capital investment a long time before materials are required for the market. Given the uncertainties in clinical trial outcomes, it is likely that several companies have invested in building manufacturing facilities for a product that eventually failed to reach the market. Under such circumstances, CMOs can provide a solution to respond to changing capacity needs caused by development uncertainties.

The batch cost of using a CMO to produce mAb is estimated at $3 million at the 15,000L bioreactor scale (Kelley 2009). Unlike using in-house facilities, the payment to a CMO is up-front and upon delivery, therefore creating discrete cash flow rather than continuous cash flow. But compared to building in-house GMP standard large-scale manufacturing facilities, the cost of using a CMO is significantly less.

1.4 SALES OF EXISTING APPROVED HUMANIZED AND FULLY HUMAN MAB THERAPEUTICS

The sales data of existing approved humanized and fully human mAb therapeutics were extracted from published reports from the innovator companies. Revenues from selling the products across all existing markets were included in the annual sales figure, some of which were transformed into US dollars using the exchange rate in the corresponding year when the report was produced. These consolidated sales figures for approved humanized and fully human mAb therapeutics from 1998 to 2009 are presented in Table 1.8. Among these FDA approved mAbs, Humira, Avastin, Tysabri, Synagis, Lucentis and Herceptin can be categorized as blockbusters (annual sales exceeds $1 billion), Vectibix, Campath, Cimzia, Raptiva and Xolair can be categorized as medium products (annual sales exceeds $100 million), while Zenapax and Soliris can be categorized as niche products (annual sales below $100 million).

Table 1.8 Annual sales of FDA approved humanized and fully human mAb therapeutics (unit: $ million for all products except Soliris, $ for Soliris).

Brand name	Approval year	Type	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
Humira	2002	human						280.0	852.0	1400.0	2000.0	3000.0	4500.0	5500.0[a]
Vectibix	2006	human									39.0	170.0	153.0	233.0[b]
Campath	2001	humanized				27.1	76.4	125.3	77.0[c]					
Avastin	2004	humanized							554.5	1132.9	1746.0	2296.0	2686.0	6117.0[d]
Cimzia	2008	humanized											13.5	109.5[e]
Zenapax	1997	humanized		19.0		30.3	32.1	30.8	35.7[f]					
Soliris	2007	humanized										66381	259004	386800[g]
Raptiva	2002	humanized						1.4	56.3	79.2	90.0	107.0	108.0[h]	
Tysabri	2006	humanized									38.1	342.0	813.0	1059.2[i]
Xolair	2003	humanized						25.3	188.5	320.6	425.0	472.0	517.0	601.9[j]
Synagis	1998	humanized	109.8	293.0	427.0	516.0	667.8	849.3	942.3	1062.9	1065.0	618.0	1230.0	1082.0[k]
Lucentis	2006	humanized									380.0	1208.0	1761.0	2397.0[l]
Herceptin	1998	humanized	30.5	189.9	321.4	488.5	774.1	934.1	1258.8	1650.8	3245.5	4256.1	4506.2	5145.6[m]

(Continued) Note: a – figures extracted from Abbott annual report; b – figures extracted from Amgen annual report; c – figures extracted from ILEX Oncology annual report; d – figures extracted from Genentech annual report from 2004 to 2008, 2009 figure extracted from Roche annual report adjusted by exchange rate CHF:USD; e – figures extracted from UCB annual report adjusted by exchange rate EUR:USD; f – Roche annual report adjusted by exchange rate CHF:USD; g – figures extracted from Alexion annual report, in $; h – figures extracted from Genentech annual report from 2003 to 2008 and Roche annual report 2009, adjusted by exchange rate CHF:USD; i – figures extracted from Elan annual report; j – figures extracted from Genentech annual report from 2003 to 2008 and Roche annual report 2009, adjusted by exchange rate CHF:USD; k – figures extracted from MedImmune annual report from 1998 to 2006 and AstraZeneca annual report from 2007 to 2009; l – figures extracted from Genentech annual report from 2006 to 2008 and Roche annual report 2009 adjusted by exchange rate CHF:USD; m – figures extracted from Genentech annual report 1998 and Roche annual report from 1999 to 2009 adjusted by exchange rate CHF:USD.

1.5 MODELING AND OPTIMIZATION APPROACHES

Optimization of portfolio management decisions for the development of new biopharmaceuticals requires an accurate and comprehensive capture of the critical factors involved in this process. Modeling and simulation techniques using fast programming tools are capable of incorporating numerous critical factors and constructing inter-relations of these factors, as well as the uncertainties. Therefore, by providing fast construction of real case scenarios, decision-makers can see the consequences of alternative choices. Beyond that, using heuristic optimization algorithms, these alternatives can be compared, selected and combined in such way that advanced solutions can be generated. Optimization of decisions, or combination of decisions is made possible by combining model simulation with optimization algorithms.

Portfolio management and capacity planning are vital to the success of pharmaceutical and biopharmaceutical developers. Hence there is a need for suitable tools that facilitate the decision-making process in these fields. Simulation-based tools are useful due to their ability to generate the likely outcomes of a given decision, from which further analyses can be performed. Rajapakse et al. (2005) proposed a computer-aided simulation tool to model the biopharmaceutical drug development pathway, comparing portfolio NPVs of various decision-making scenarios. A further study incorporating

Monte Carlo simulation to capture the inherent uncertainties in drug development such as development time, COG, and yield, was developed to more accurately establish portfolio risk-reward characteristics (Rajapakse et al. 2006). George et al. (2007) proposed a multi-criteria decision-making framework to provide a holistic evaluation of capacity sourcing decisions from both financial and operational perspectives. While simulation-based tools have demonstrated their capability of linking a decision with its outcomes, the decision-maker is usually confined to the limited choices provided by the scenario analysis. Therefore, optimization-based tools were developed to search large decision spaces for the optimal decisions that otherwise may be hidden from the decision-maker. Broadly, these optimization tools use either mathematical programming methods or heuristic algorithms. The former transforms the problem into mathematical formulas and feeds them into a computational solver for optimal solutions, whereas the latter makes slight modifications to existing decisions in an iterative fashion based on concepts such as evolutionary selection.

Mathematical programming is often applied to the capacity planning and supply chain management problems. Papageorgiou et al. (2001) proposed an MILP formulation of pharmaceutical supply chain management problem that takes into account the manufacturing of API and the global trading structures. This deterministic model is capable of processing up to 8 products in the company's portfolio. Further developments of the tool enabled it to capture the uncertainty in demand (Levis & Papageorgiou 2004) and clinical trial outcomes (Gatica et al. 2003). Sousa et al. (2011) improved this tool's capability in processing long-term strategic planning problems with large portfolio and multi-production sites by implementing a decomposition algorithm with MILP. Lakhdar et al. (2006) developed a biopharmaceutical supply chain management tool for planning and scheduling of multiple products in a single facility using MILP, with a focus on facility utilization and cost reduction. This tool was later improved by adding the capability to process multi-facility problems under demand uncertainty, as well as to pursue more objectives such as customer service level (Lakhdar et al. 2007). Siganporia et al. (2013) proposed an MILP

approach to address multi-site production planning of biopharmaceutical products with either fed-batch or perfusion bioprocesses. However, the analysis was based on fixed product candidates. There have been no previous studies focusing on scenarios in which the decision-maker is exposed to portfolio selection problems with given manufacturing facilities.

Despite the development of mathematical programming-based optimization tools in capacity planning and supply chain management fields, it is not used as often in portfolio management scenarios. This may be due to the difficulty of translating pipeline development performance into mathematical formula. Mathematical programming does not easily provide information beyond the optimal decisions, which could be obtained by running a simulation-based tool with the given decision. To solve this problem, several tools combining mathematical programming with discrete-event simulation in portfolio management scenarios were developed (Subramanian et al. 2000; Varma et al. 2007).

The other approach uses evolutionary algorithm as the heuristics, making use of simulation-based tools and optimizing the decisions based on the feedback from the simulation process. Blau et al. (2004) developed a portfolio management tool with a genetic algorithm to select the optimal candidate combination and sequence of development. George & Farid (2008a) proposed a stochastic optimization framework that incorporates decisions in portfolio selection, activity scheduling, and outsourcing in clinical research and manufacturing. Probabilistic model building genetic algorithms using Bayesian networks were used here to solve the combinatorial optimization problem. The tool optimizes the solutions towards higher potential reward in terms of portfolio ENPV and lower risk of NPV below zero. This tool was extended to be capable of incorporating a minimum NPV constraint in its optimization process (George & Farid 2008b).

Although these studies have demonstrated the possibilities of using various tools to push the boundaries of portfolio management and capacity planning, they have not focused on the consequences of the optimal solutions on the

budget distribution across the various activities such as clinical trials, manufacturing, and process development. Importantly, these details are essential to benchmark and enhance the understanding of the implications of certain decisions.

Simulation and optimization techniques are also featured in mAb process economics tools. Farid et al. (2005) developed a decision-support tool for antibody manufacturing to facilitate the decision between stainless steel and disposable facilities under different product demands and titres. Lim et al. (2006) compared fed-batch with perfusion culture for mAb processing from COG and capital investment perspectives. This approach incorporates the uncertainties in titre and yield with Monte Carlo simulation. Pollock et al. (2013) made use of stochastic discrete-event simulation to compare process economics between fed-batch and perfusion cell culture. Using the same technique, Stonier et al. (2012) developed a decision-support tool to assess the process robustness of chromatography options used in antibody purification. MILP and MINLP were also featured in biopharmaceutical facility design, especially in optimal chromatography process design (Liu et al. 2013a; Liu et al. 2013b). Simaria et al. (2012) developed a multi-level decision-making tool using genetic algorithms to facilitate chromatography sequence and column size optimization. Allmendinger et al. (2014) introduced an evolutionary algorithm for optimizing mAb purification chromatography sequence and column sizing towards multiple objectives including COG/g, process robustness, and capability of removing the impurities.

The decision-maker can also make use of several commercially available solutions for optimization and simulation purposes. The Decision Tools Suite from Palisade is a general-purpose decisional tool based on Microsoft Excel, which uses Monte Carlo simulation for stochastic modeling, and is capable of implementing decision tree, neural networks, and evolutionary algorithms for various decision-making scenarios. As the tool is Excel-based, it is not ideal for performing rapid data manipulation on a large scale, though it can be useful for product prototyping. Phoenix from Certara (formerly Pharsight) is a clinical trial modeling software platform for

processing pharmacokinetic, pharmacodynamics, and toxicokinetic data. Aspen Economic Evaluation package from Aspentech is a multipurpose chemical process optimization and economic evaluation software. BioSolve from Biopharm Services, a biopharmaceutical manufacturing process simulation software based on Microsoft Excel, provides the user with the flexibility of changing scale from lab to commercial, and is capable of rapidly establishing processes that can be configured as vaccine or mAb processes. It creates a dashboard-like process report that includes economic metrics.

1.6 AIM AND ORGANIZATION OF THESIS

The previous sections presented a description of the main subjects of the biopharmaceutical drug development process that are involved in portfolio management decision-making, emphasizing the key factors and methodology that drive the decision-making process. Modelling and optimization approaches addressing the above factors are reviewed with attention to their techniques and application scenarios. Despite the coverage of existing research on the subject, a portfolio management decision-making tool that provides full flexibility towards candidate selection and provides reports on critical portfolio cost characteristics for capacity and budget planning is still absent.

The aim of this thesis is therefore to develop computational decision tools that produce quality solutions to biopharmaceutical portfolio management problems under changing circumstances, and to provide guidance to the related implementation issues from a cost evaluation prospective. The remainder of the thesis is structured around achieving this goal.

In Chapter 2, a drug development lifecycle cost model is proposed for the purpose of cost evaluation of biopharmaceutical portfolio development. Monte Carlo simulation and dynamic simulation mechanisms are integrated in this activity-based, object-oriented tool to enable the capability of allocating resources under development uncertainties. A bespoke multi-objective evolutionary algorithm is created so as to optimize portfolio

management decisions based on their calculated risk-reward characteristics. Features such as the data management system that produces reports regarding the performance of solutions, and the details of the drug development process are also described in this chapter.

Cost evaluation of biopharmaceutical portfolio development using the drug development lifecycle cost model is presented in Chapter 3. Benchmarks of industrial average costs of developing a single product and a portfolio of products aiming at one market success per year are generated, with special attention to the cost spent on non-clinical activities. Scenarios that feature optimistic and pessimistic assumptions of drug success rates are also investigated, with various sources of out-of-pocket development costs. An analysis of the implications of drug development delay in the portfolio context discovers the cost of managing the delay at a tolerable level.

Based on the cost benchmarks produced in Chapter 2, the implementation of the stochastic optimization tool for biopharmaceutical portfolio management decision-making is presented in Chapter 3. A hypothetical candidate pool is formulated with products of distinct risk-reward characteristics. Portfolio management decisions are optimized under various budget and capacity constraints, and the trends of optimal solutions are investigated, as well as their cost distribution details across the development timeline. The candidate pool is further diversified by introducing product candidates that are more advanced in the development process, but require upfront cost to develop. Optimization of portfolio management decisions under different budgets and upfront payments is explored, with the analysis on critical decision boundaries regarding the acquisition of outside products.

In Chapter 5, the application of the drug development lifecycle cost model focuses on the emerging cell therapy industry. The differences in clinical trial, manufacturing, and process development activities between cell therapy and biopharmaceutical products are reviewed and the related costs are estimated. Cost evaluation of cell therapy portfolio development is performed and the results compared against those for biopharmaceuticals. Estimations of cell therapy market potential and gross margin are made to

extend the analysis of portfolio expected NPV and its vulnerability against delays in late stage development due to the potential market competitions.

Finally, Chapter 6 summarizes the main contribution of this work and discusses likely directions for future work.

CHAPTER 2

COMPUTATIONAL DECISION TOOLS FOR STOCHASTIC OPTIMIZATION AND COST EVALUATION OF BIOPHARMACEUTICAL PORTFOLIO DEVELOPMENT

2.1 INTRODUCTION

As discussed in the previous chapter, studies on biopharmaceutical cost modelling have been focusing on total stage costs and overall out-of-pocket and capitalized costs, rather than how these costs distribute across clinical and non-clinical activities. In this chapter, a drug development lifecycle cost model is proposed to capture the cost distribution characteristics in drug portfolio development by decomposing drug development stages into clinical trials, manufacturing, and process development activities. More detailed implementations of this cost evaluation tool are presented in Chapter 3 and Chapter 5, featuring portfolio development of pharmaceutical, biopharmaceutical, and cell therapy products.

Based on this drug development lifecycle cost model, an improved portfolio development model was designed, with Monte Carlo simulation to capture the effect of uncertainties and dynamic simulation to model the resource allocation process. This model was implemented as the evaluation engine of the stochastic optimization tool, which could be used to support portfolio management decision-making by providing appraisals for strategic decisions. A multi-objective evolutionary algorithm (MOEA) was adapted from the publicly available jMetal package (Durillo & Nebro 2011) and tailored to facilitate the decision-making of biopharmaceutical portfolio management. The algorithm inherits the concept of NSGA-II (Deb et al. 2002) and uses NPV distributions provided by the portfolio development model as objectives for optimization. A binary string representation of decision variables was designed as the solution structure to allow the selection of any number of product candidates into the R&D portfolio. The

implementation of this stochastic optimization tool is presented with various candidate pools in Chapter 4.

The remainder of this chapter is structured as follows. Section 2.2 describes the overall structure of the optimization tool, whose main components are separately described in the following 3 sections. The evaluation engine based on the drug development lifecycle cost model is discussed in Section 2.3. The adaptation of MOEA and its working process is described in Section 2.4. The design of the output formats of data reports generated by the stochastic optimization tool, as well as the tool for data visualisation, are presented in Section 2.5.

2.2 THE OVERALL STRUCTURE OF THE STOCHASTIC OPTIMIZATION TOOL

The stochastic optimization tool for strategic portfolio decision-making in biopharmaceutical new product development is comprised of 3 functional components: 1) an optimization algorithm, for generating and optimization the strings representing portfolio management solutions, which can be evaluated in 2) the evaluation engine, for evaluating the quality of solution by constructing the portfolio development process and simulating cash flow performance under resource constraints and uncertainties; and finally, the results from the aforementioned components are collected and analysed by 3) a data management system. A detailed diagram illustrating the interactions of these 3 components is presented in Figure 2.1.

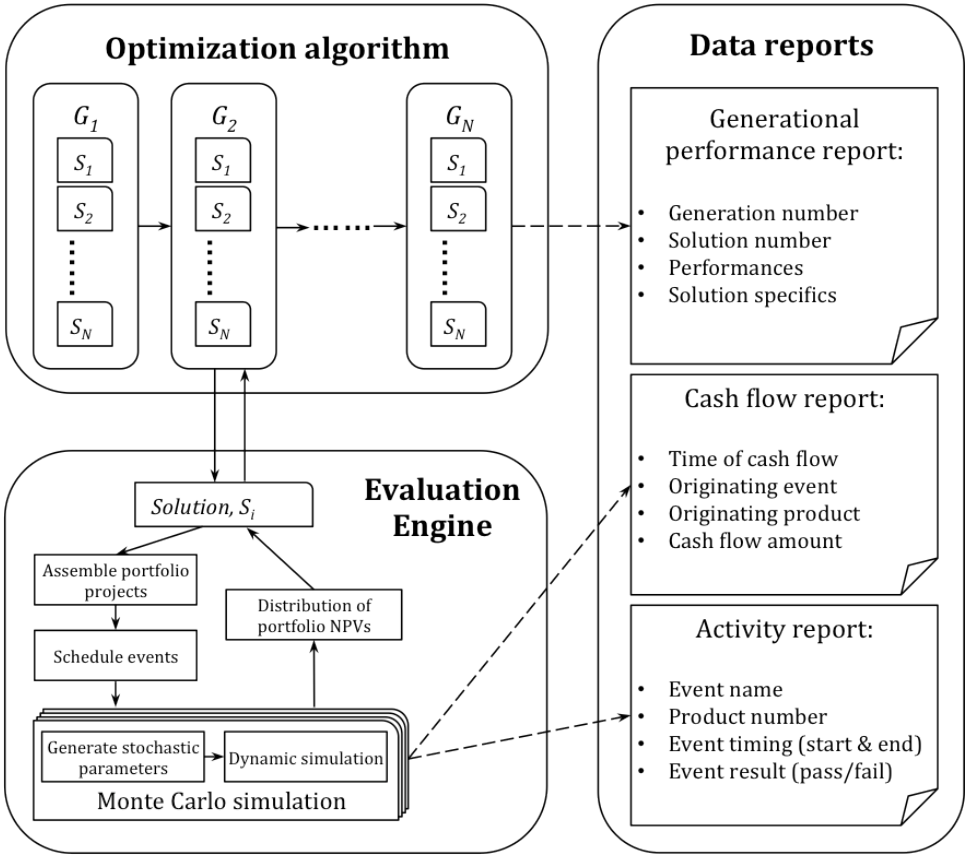


Figure 2.1 The overall structure of the stochastic optimization tool for biopharmaceutical portfolio management decision-making..

The tool is comprised of 3 major functional components: 1) an evaluation engine capable of performing Monte Carlo simulation and dynamic simulation in order to evaluate the quality of solutions under resource constraints and uncertainties; 2) A multi-objective evolutionary algorithm (MOEA) for optimizing solutions by iteratively replacing the parent solutions within the generation with better offspring; and 3) a data management system that collects information concerning the performance of each generation, the cash flow, and the details of activities for each Monte Carlo simulation.

Several prototypes of the stochastic optimization tool were built either in Java or in Excel with proprietary add-in for evolutionary algorithm and Monte Carlo simulations. The pros and cons of these modelling alternatives are presented in Table 2.1. Java was chosen as the modelling environment primarily due to its flexibility and high performance, in particular the object-oriented features that facilitate the design of activity-based portfolio development lifecycle, although it lacks instant database solution and data visualization tools. Nonetheless, Excel was useful for model prototyping since its build-in formulae and charts allow quick analysis of the results, which can help understanding model logics and identifying key design pitfalls.

Table 2.1 Pros and cons for Java and Excel as modelling environment.

Java	Excel
Object-oriented, highly flexible	Spread-sheet based, semi-flexible (require using VBA for in-depth design)
Professional package for implementing evolutionary algorithm, available for public	Proprietary add-ins for genetic algorithm
High performance with Java virtual machine	Relatively slower
Portable, cross-platform	Available exclusively on PC and Mac systems
No integrated database	Integrated database with spread-sheet functionality
Requires outside tools for data analysis and visualization	In-house data analysis and visualization
Requires outside tools for collaborative development	Collaborative development achieved by Microsoft online services

Note: The features of Java programming language described here is representative for most object-oriented programming language such as C#. Most of the features of Excel in this table can also be used to describe numerical computing tools such as MATLAB in terms of modeling biopharmaceutical portfolio development.

2.3 THE EVALUATION ENGINE

The role that the evaluation engine played in the stochastic optimization tool was to provide an assessment of a single solution in terms of two key statistics of the NPV distribution, namely the average positive NPV and the probability of NPV being positive. A drug development lifecycle cost model was developed as the backbone of the evaluation engine that provided fast characterization of cost distributions of portfolio development for certain product categories. The model first established development pathways for products within the portfolio, then scheduled all related activities of clinical trials, manufacturing, and process development for either cost evaluation, or the more sophisticated Monte Carlo simulation if stochastic optimization was required. A schematic of the running mechanism of the evaluation engine is presented in Figure 2.2, in which the drug development lifecycle cost model is surrounded by dash lines.

As illustrated in Figure 2.2, the scope of simulation and modelling for this evaluation engine was limited to the activity level and above. The core elements of simulation were the components of drug development lifecycle, namely the clinical trial, manufacturing, and process development activities. This evaluation engine did not model the manufacturing process of a particular product explicitly, nor did it model the supply chain characteristic for transferring bulk materials from manufacturing facilities to clinical trial sites. Under the scope of this work, the more detailed simulations were considered to be of little impact to the overall performance of portfolio development decision-making, though they do matter in reality. Variations generated in Monte Carlo simulations regarding the durations and costs of activities can be seen as the results of different manufacturing practises or supply chain management decisions. Therefore the user can place his/her attention on the drug development lifecycle activities and how they interact with the resource constraints.

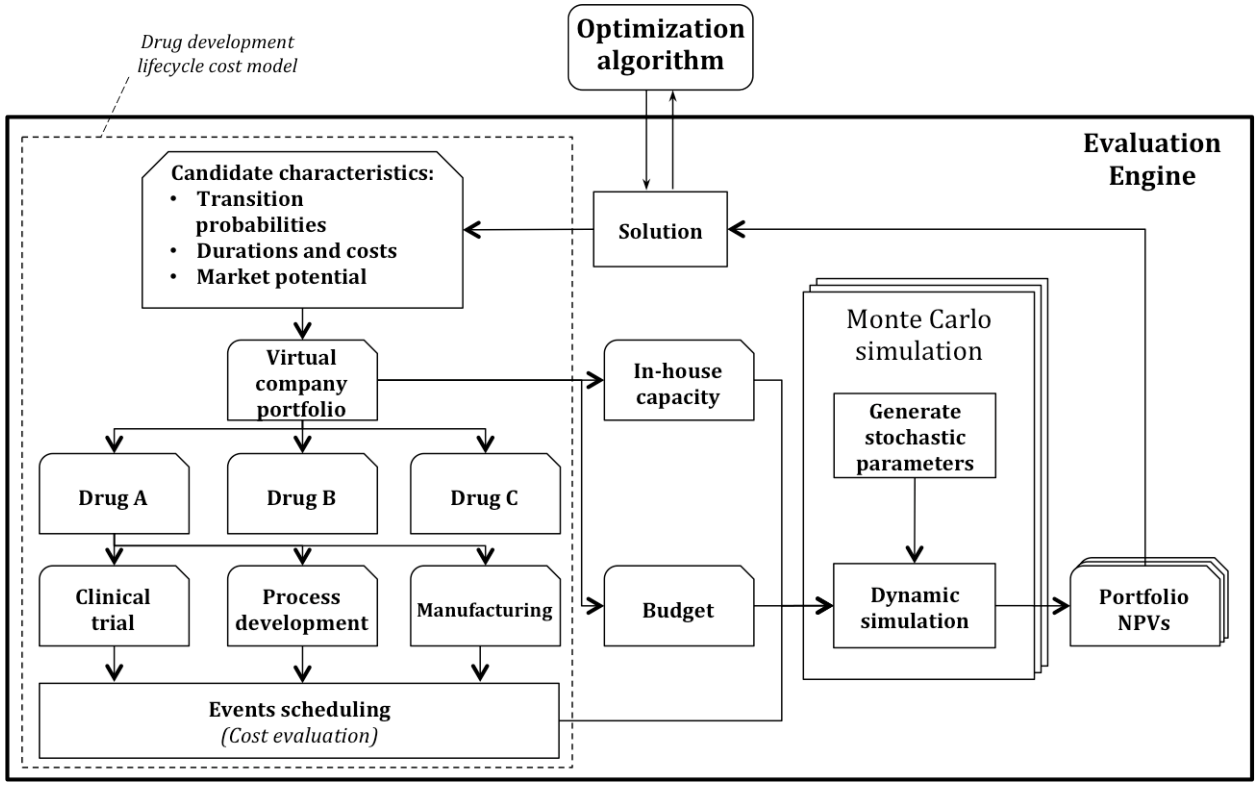


Figure 2.2 The evaluation engine of the stochastic optimization tool..

The evaluation engine was built upon the drug development lifecycle cost model (the part surrounded by dash line). Development pathways of portfolio drugs were constructed for newly generated solutions, and simulated in dynamic simulation under capacity and budget constraints as well as development uncertainties. The resulting portfolio NPV distribution was returned as appraisal to the solution.

2.3.1 The drug development lifecycle cost model

The design of the drug development lifecycle cost model followed a top-down, activity-based approach. It created objects to represent the drug developing company, the drug candidates, and the activities that needed to be carried out in the development lifecycle. The object-oriented design of the classes is described in the following paragraphs, focusing on their specific fields and methods. The description format in these paragraphs also follows the naming convention that uses concatenated words each starting with upper case to represent class names, and lower case separated by underscores to represent object and method names.

Table 2.2 presents the key aspects in designing the "Company" class for the drug development lifecycle cost model. This class has its specific attributes such as the list of portfolio products and manufacturing facilities. It also functions to assemble portfolio products based on the values of decision variables. The resource attributes, i.e. the budget and manufacturing facilities, were inactivated during cost evaluation process.

Table 2.2 Key aspects of object-oriented design of the "Company" class.

Field type	Field name	
String	name	As the identifier of the company object.
List<Drug>	drugs	The list of portfolio products.
Budget	budget	The company's annual R&D budget.
double	cost_of_capital	The discount factor employed by the company for calculations of DCF and NPV.
List<ManuFacility>	mfs	The list of manufacturing facilities within the company.
Method return type	**Method name (argument)**	
void	assemble_drugs (int[] decisions)	Take portfolio management decisions as input, assemble drugs into development portfolio.

Note: The fields and methods presented in this table do not include common object-oriented programming elements such as object constructor.

Following the construction of a company object, several drug objects were created with key design aspects described in Table 2.3. Drug specific attributes such as starting stage and market potential were included, as well as the method to assemble all relevant development activities from clinical trial, manufacturing, and process development into a list of activities.

Table 2.3 Key aspects of object-oriented design of the "Drug" class.

Field type	Field name	
int	drug_number	As the identifier of the drug object.
int	starting_stage	The starting stage of drug, represented by integer indexing of development stages. e.g. "starting_stage = 0" means the drug starts at pre-clinical stage.
double	market_potential	The value of the drug should it receive FDA approval.
List<Activity>	activities	The list of activities that included in the drug development lifecycle.
boolean	successful	The result of drug development for a given Monte Carlo simulation. This and the following 2 attributes are reset for every Monte Carlo simulation.
int	time_to_market	The time of drug receiving FDA approval to market.
int	current_stage	The current development stage of the drug. It is updated every time the drug enters another development stage.
Method return type	Method name (argument)	
void	assemble_activities()	Construct the drug development lifecycle by assembling activities of clinical trial, manufacturing, and process development.
void	reset()	Reset the drug development status for every Monte Carlo simulation.

Note: The fields and methods presented in this table do not include common object-oriented programming elements such as object constructor.

There were fields reserved for the drug object to record its development status during the running of Monte Carlo simulations including the result of development, the timing of product market approval, and the current stage of development. These fields were reset for every Monte Carlo simulation and inactivated when running the application for cost evaluation purpose.

Activities created by the drug objects can be divided into 3 distinct sub-classes, clinical trial, process development, and manufacturing. They were all inherited from the abstract "Activity" class described in Table 2.4. The key features that the design of the "Activity" class enables in drug development lifecycle cost model were the capability of distinguish costs from various origins and fast scheduling of activities according to their dependencies. Once the scheduling of activities was finished, portfolio development cash flow can be generated for cost evaluation purpose.

A large portion of design aspects of the "Activity" class was dedicated to accommodate Monte Carlo simulation and dynamic simulation in stochastic optimization. This included the actual timing of activities, the mechanisms regarding the triggering, progression, and finishing of the activities, and interruptions whenever the project fails. These are discussed in the following sub-sections.

Table 2.4 Key aspects of object-oriented design of the "Activity" class.

Field type	Field name	
Drug	drug	The drug it belongs to.
int	stage	The integer indexing of development stage it belongs to.
String	activity_type	The type of activity (clinical trial, manufacturing, or process development).
int	duration	The duration of activity.
int	cost	The total cost of activity
boolean	starting	If the activity is the starting activity of development lifecycle.
Activity	next	Next activity.
int	time_start	The planned starting time of activity.
int	time_start_s	The actual starting time of activity. For each Monte Carlo simulation, the starting time of activity can be different due to delays from previous activities or lack of resources.
int	time_end_s	The actual end time of activity.
int	elapsed_time	The actual elapsed time of activity during dynamic simulation.
boolean	triggered	Record the status of activity during dynamic simulation.
Method return type	Method name (argument)	
boolean	triggering()	Checking if the conditions of activity starting are met. If yes, start the activity.
int	progressing()	Activity progression in dynamic simulation. Effective progression returns the associated cost and increases the elapsed time of activity.
boolean	interrupted()	The activity gets interrupted when product fails in clinical trials.
boolean	finishing()	Activate the finishing process when elapsed time equals the duration of activity.
void	reset()	Reset development status.

Note: The fields and methods presented in this table do not include common object-oriented programming elements such as object constructor or the ones created for data collection purposes.

2.3.2 Monte Carlo simulation

Monte Carlo simulation is implemented here to address the uncertainties in the various stochastic inputs, including clinical trial lengths and costs, product market potentials, and most importantly, the pass/fail result of clinical trials. Random values are generated to represent such uncertainties based on assumptions of their distributions. For quantitative stochastic parameters such as duration of activities, product market potential, and costs, this tool is capable of generating random numbers following Gaussian, triangular, and Poisson distributions, the selection among which can be altered by user requirement. For the pass/fail result of clinical trials, the tool generates binary random values based on the phase transition probabilities.

The random values are only generated when they are needed for efficiency consideration. Since during the simulation of portfolio development process many activities may not even be triggered, it would be a waste of computation time to prepare random values for their stochastic parameters. The market potential information is generated when the drug obtains FDA approval. Similarly the costs and durations of activities are generated only when the activities are triggered, and the pass/fail results of clinical trials are generated at the end of clinical trials. The random values are removed once a new Monte Carlo simulation is initiated by the "reset()" method included in the key design aspects of company, drug, and activity classes. At the same time, a new random number generator is created with a different seed to maintain the randomness.

To determine the sufficient number of Monte Carlo simulations needed for providing full coverage of NPV distributions, the running average of portfolio NPV is analysed for 20 distinct solutions with uncertainties from clinical trial results. Figure 2.3 shows the convergence of NPVs as the number of Monte Carlo trials increases. In most situations, the NPVs converge before 100 trials. Increasing the number of Monte Carlo simulations from 100 provides little improvement in terms of capturing the distribution of NPVs. However, it may be necessary to re-configure the

number of Monte Carlo trials as the level of uncertainty changes, or when additional mechanism that complicates the process is introduced.

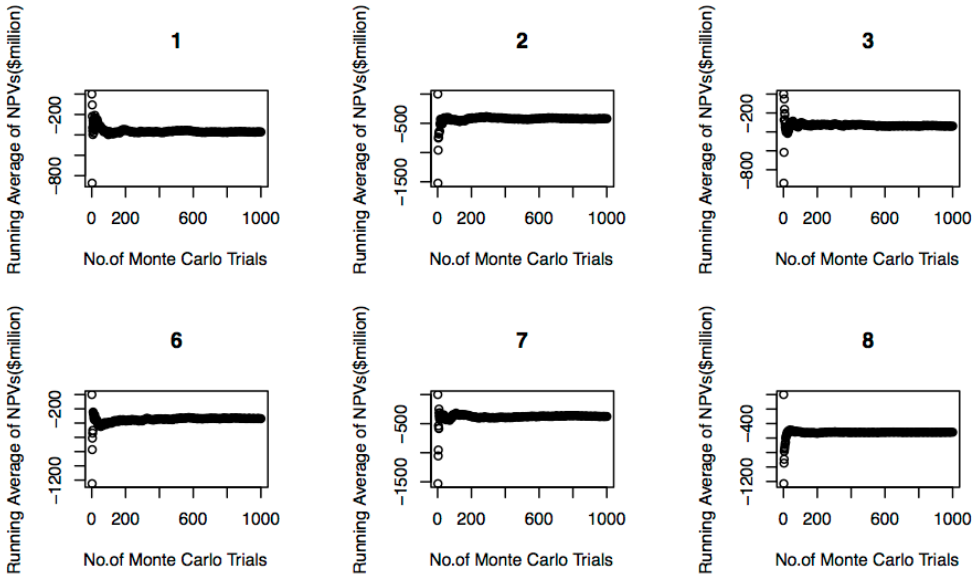


Figure 2.3 Cumulative running averages of NPVs throughout multiple Monte Carlo simulations.

This is a fraction of a bigger graph consists of 20 cumulative running average plots for 20 different solutions. The x-axis is the number of Monte Carlo trials and y-axis is the cumulative running average of NPVs for existing number of Monte Carlo trials.

2.3.3 Dynamic simulation with resource constraints

The introduction of uncertainties makes it impossible to predict the exact timing of activities during the simulation of biopharmaceutical portfolio development process. The problem is further complicated by the requirement to allocate resources between activities based on their timing precedence. Therefore, a dynamic simulation approach was proposed under the activity-based framework of drug development lifecycle cost model to represent how biopharmaceutical portfolio development takes place. This approach breaks up the time into small slices and updates the states of activities by moving the time horizon from one slice to another.

This approach can be implemented by using commercial simulation packages capable of dynamic continuous simulation like ExtendSim.

However, the software is overly complex compared to the simulation requirement of this approach. It is not economical to make the purchase without using most of its functions. In addition, the level of control over the simulation process cannot be fulfilled by the proprietary software without the proper application interface with other modules of the tool. Therefore dynamic simulation is purposely built into this tool.

Before initiating the dynamic simulation, critical starting times need to be established for activities that do not depend on other activities to start. This is accomplished by the scheduling procedure in the drug development lifecycle cost model, and is based on the planned durations of and the dependencies between the activities. The dynamic simulation process takes the planned starting time of the independent activities as their actual starting time. For other activities, their timings will be determined during the running of dynamic simulation. The scheduling procedure runs only once during the evaluation of one solution for efficiency considerations.

The Monte Carlo simulations start when the scheduling procedure finishes. For each Monte Carlo simulation, the dynamic simulation moves the time horizon from the starting point of portfolio development to a given future time specified by the user.

The dynamic simulation implemented here updates all activities for each time slice by invoking their triggering, progression, and finishing mechanisms, which were built into the model. Activities are divided into categories where they inherited the abstract methods from the "Activity" class, but the implementation of these methods differs. The three major categories and their mechanisms are presented as follows.

- *Category 1: Clinical trials*

The clinical trial activity category includes all the activities that trigger a pass/fail judgment at the end of their duration. By this definition, activities such as pre-clinical trials and FDA reviews are also included in this category, even though they are not actual clinical trials. Another feature of clinical trial activities is that they are normally on the drug development

critical path. The triggering, progression and finishing mechanisms of clinical trial activities are shown in Figure 2.4.

The triggering mechanism first checks if the activity is already triggered, and if not, it will then check if the activity meets the triggering conditions. For clinical trial activities, the triggering conditions normally include 1) the corresponding manufacturing activity has finished to supply the required material, and 2) the previous clinical trial has finished and the result is successful. All satisfied, the clinical trial activity is then triggered, and the actual start time is set to the current time and activity elapsed time is set to 0.

For an already triggered clinical trial activity, the progression mechanism is activated instead. Progression mechanism checks if there is enough budget left for the activity to carry on. If yes, the consumption is deducted and the progression is recorded by increasing the elapsed time by 1 unit time. The mechanism also reports the incurring cost to cash flow data collection.

The finishing mechanism is invoked once the activity elapsed time equals its duration. For a clinical trial activity, the pass/fail result is produced by generating a uniformly distributed random number between 0 and 1 and comparing it to the phase transition probability of the activity. If the latter is smaller, the activity fails. The finishing mechanism also sets the current time as the activity's actual end time and changes the value of end status to true to prevent re-invoking the progression mechanism in the next unit time. If the activity passes, the triggering condition will be changed for the next activity. Otherwise the finishing mechanism will shut down the project by calling the "interrupted" method of all concurrent activities for this product.

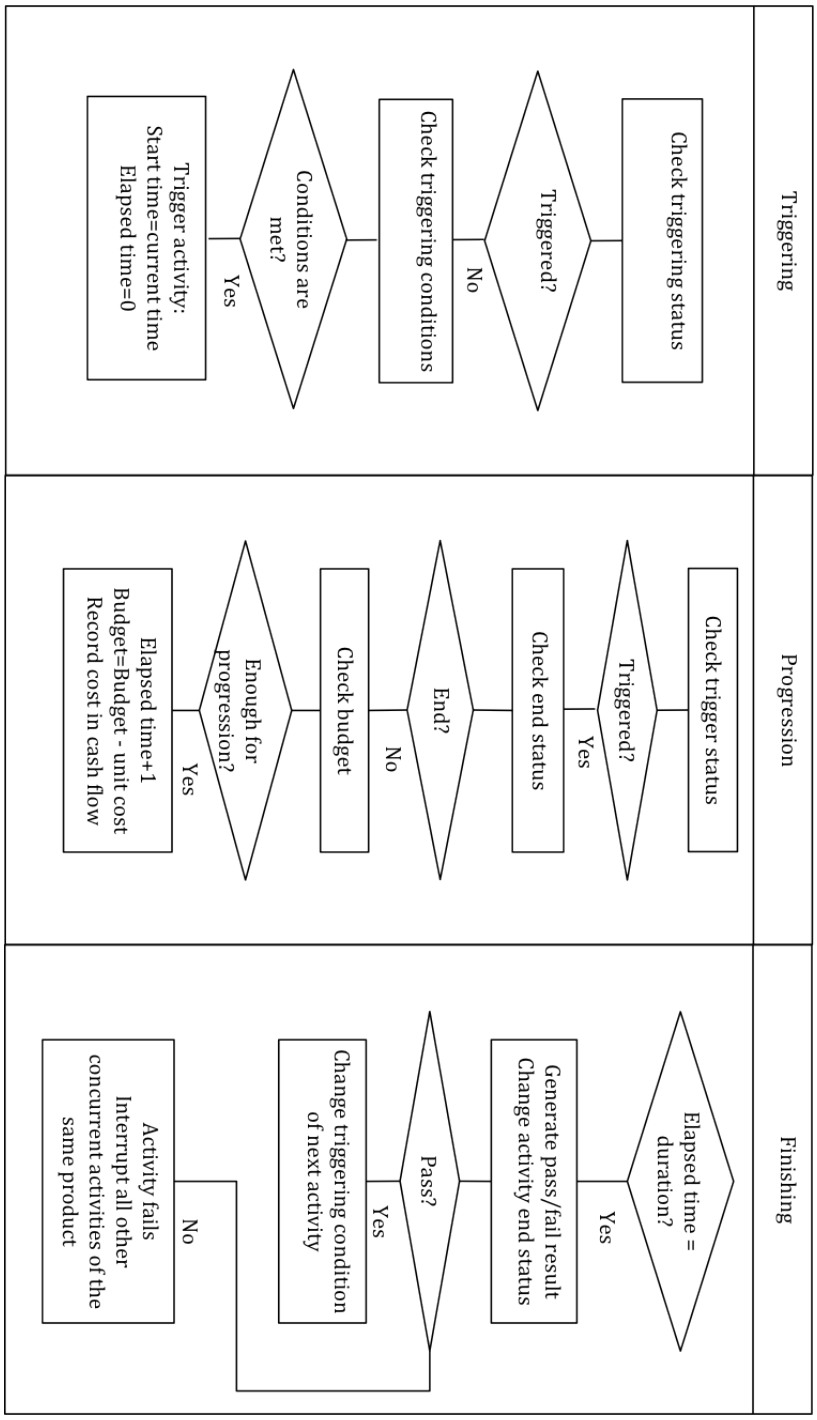


Figure 2.4 The triggering, progression, and finishing mechanisms of clinical trial activities in dynamic simulation.

Square frame represents an operation. Diamond frame represents a judgement.

- *Category 2: Manufacturing*

Manufacturing activities are defined as the activities that require manufacturing facilities to start. The design of the dynamic simulation mechanisms of manufacturing activities is presented in Figure 2.5.

Similar to clinical trial activities, the triggering mechanism of a manufacturing activity first checks if the activity is already triggered, then checks if the activity meets its triggering conditions, which in this case is the successful completion of corresponding process development activity. The triggering mechanism of manufacturing differs from that of clinical trials in that even if all conditions are satisfied, it requires spare facility to start. The idle facility that the company has access to will be marked "occupied" once it undertakes the manufacturing activity. The progression mechanism of manufacturing activities is exactly the same as the one of clinical trial activities. The finishing mechanism is invoked once the elapsed time equals the duration of activity. The finishing of manufacturing activity does not require randomly generated number to decide whether the activity is successful; instead, it releases the manufacturing facility by changing its status from "occupied" to "idle" so that it is able to undertake other manufacturing tasks. Completion of a manufacturing activity changes the triggering condition of its next activity, clinical trial in most cases.

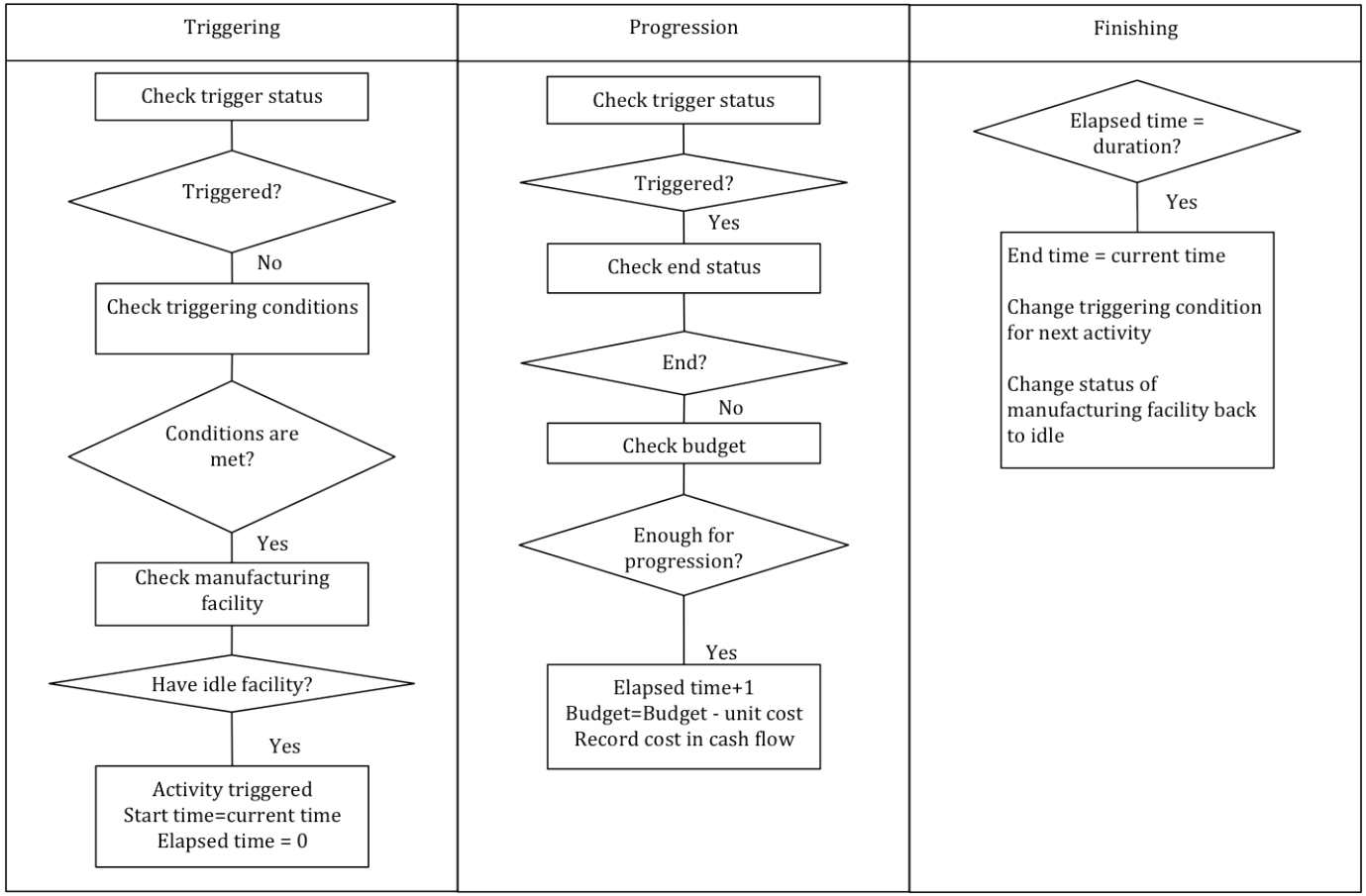


Figure 2.5 The triggering, progression, and finishing mechanisms of manufacturing activities in dynamic simulation..

Square frame represents an operation. Diamond frame represents a judgement.

- *Category 3: Process development*

Similar to clinical trial activities, the process development activities only require one resource for its progression, the budget. The key distinction of process development activities is that they do not depend on other activities to start. Their start times for dynamic simulation are established by the scheduling procedure that plans the activities based on the need of clinical trials. Hence the triggering condition for process development activities only requires that the current time is the planned start time.

Figure 2.6 illustrates the state changes for activities from clinical trial, manufacturing, and process development in an example of dynamic simulation. Activity A and C are triggered from the start because they require no previous activities. They remain triggered until unit time 3 when Activity C is finished, which changes the triggering condition for its successor, Activity D. When unit time 4 hits, Activity D is triggered as its triggering conditions are met. In this particular example, because the length of Activity D is only 1 unit time, the finishing time of Activity D coincides with that of Activity A, making all triggering conditions satisfied for Activity B. Had the random generator produced a slightly longer duration for Activity D, Activity B would be delayed due to a lack of material supply from its corresponding manufacturing activity. On the other hand, if Activity A lasts a little longer, Activity B can not be triggered either since one of the triggering conditions for clinical trials is that the previous trial must have finished. At unit time 5, Activity B is triggered and it progresses through the rest of unit times in the diagram. The states of Activities A, C, and D are all "end" so their progression mechanism cannot be activated.

The setup of the tool defines that the durations of activities are positive integer values, with the unit time being 1 week. Therefore, the durations of activities illustrated in Figure 2.6 are all multiples of a week. Further dividing the unit time is considered unnecessary at this level of simulation.

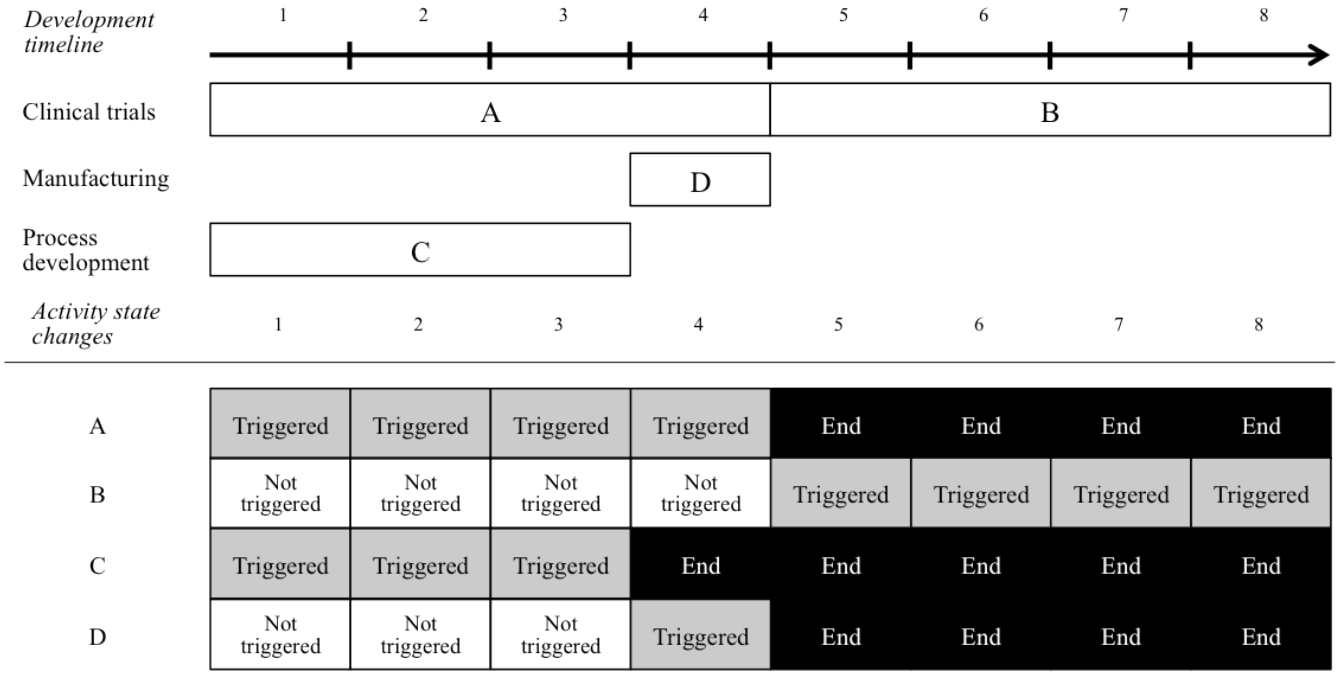


Figure 2.6 Typical state changes for activities from clinical trial, manufacturing, and process development in dynamic simulation.

For each Monte Carlo simulation, the dynamic simulation updates the states of activities by invoking the triggering, progression, and finishing mechanism for each unit time passing. Dependencies between activities and the availability of resources in terms of budget and manufacturing facility determine the triggering conditions. In this diagram, it is assumed that there are sufficient budget and facility to support activities from A to D.

2.4 THE OPTIMIZATION ALGORITHM

The purpose of optimization algorithm is to efficiently search the decisions space and find the optimal solutions based on the appraisals provided by the evaluation engine. As described in previous subsections, the simulation of biopharmaceutical portfolio development lifecycle with uncertainties and resource constraints involves complex mechanisms that pose a challenge to conceptually formulating the problem in mathematical form. With the entire evaluation engine being activity-based, a more intuitive approach is to use genetic algorithm as a search heuristic for finding the optimal solutions. This approach also has the following advantages.

- Genetic algorithm can achieve relatively fast convergence to global optimum regardless of the fitness landscape. The mutation operation performed during the replacement of the previous generation of solutions enables random drift from the local optima.
- The repeated fitness function evaluation feature of genetic algorithm fits well with the Monte Carlo simulation, as the increased number of evaluation improves the quality of fitness value. Meanwhile, the evaluation process is fast with the activity-based evaluation engine, presenting the repeated evaluation as the performance bottleneck of the tool.
- For the portfolio management problem, the design of integer-based solution structure is simple and intuitive. Unlike problems with real number solutions, integer-based solution in genetic algorithm does not need further translation. It is a direct representation of strategic portfolio management decision-making.
- Genetic algorithm produces an optimal set of solutions so that the user of this tool have more options in choosing the best strategy based on his/her preference toward implementation. This feature is particularly advantageous in the context of multi-objective optimization as competing solutions can be presented within 1 Pareto optimal front.

Despite these advantages, there are limitations that require special attention in the design and implementation of genetic algorithm. First, there are no definite termination criteria for the algorithm. The algorithm can in theory run forever without having any improvement to its optimization objectives. It is therefore necessary to arbitrarily set up a termination criteria based on the progression of convergence to a specific problem. A trial run should be performed ahead of the actual optimization and the progression of objectives should be monitored. A decision on how many generations to run can then be reached by comparing the cost of an extra generation against the benefit in terms of improvements in objectives.

Second, to maximize the performance of the algorithm, the user need to set up the running parameters for a given problem. These parameters include the crossover rate, the mutation rate, and most importantly, the size of the population. Trial runs with different combinations of these parameters should be performed ahead of optimization to explore the optimal setup that maximizes the improvement of objectives within a given number of evaluations.

Third, for some solution structures, it is possible that "illegal" solution be generated during the optimization process, i.e. solutions that are not applicable for evaluation is generated. Evolution strategies are required in dealing with these "illegal" solutions. Viable options are 1) eliminating the possibility of generating "illegal" solutions by the specific design of solution structure; or 2) fixing the "illegal" solutions so that they are applicable for evaluation; or 3) setting up penalty mechanisms when "illegal" solutions are generated.

The first 2 limitations are problem-specific. Therefore they are addressed in the implantation of the algorithm. The design of solution structure in this tool is inherently immune to the 3rd limitation as described in the following subsection.

2.4.1 Solution structure

Portfolio management decisions typically concern the selection from a group of investment assets, in this case, product candidates of various characteristics. With each individual product candidate, the key question is whether it should be in the development pipeline, given the circumstances of the decision maker. Hence a solution structure in the form of a binary string with its length equal to the number of product candidates is proposed to represent the portfolio management strategy. Each bit of this binary string represents a unique product candidate, with the value of this bit representing the decision of whether to include this product candidate into the portfolio. See Figure 2.7.

As mentioned before, this design completely eliminates any possibility of generating "illegal" solutions as long as all product candidates are eligible for development. The design of binary string as solution structure also provides utility in situations where updating product candidate pool happens frequently. The capability of embracing changes to the candidate pool matters as the ground is shifting every day in modern pharmaceutical industry with new discoveries and technologies emerge rapidly. For every new product candidate, the decision-maker can simply add it to the list of existing candidates without causing any conflicts.

Compared to a design of using integers to represent the portfolio selection decisions, the binary string representation has the flexibility of choosing any number of candidates, therefore releasing the full potential that can be achieved by the optimization algorithm. Restrictions on how many candidates to choose can also be conveniently installed onto the binary string by limiting the number of 1 value in its bits.

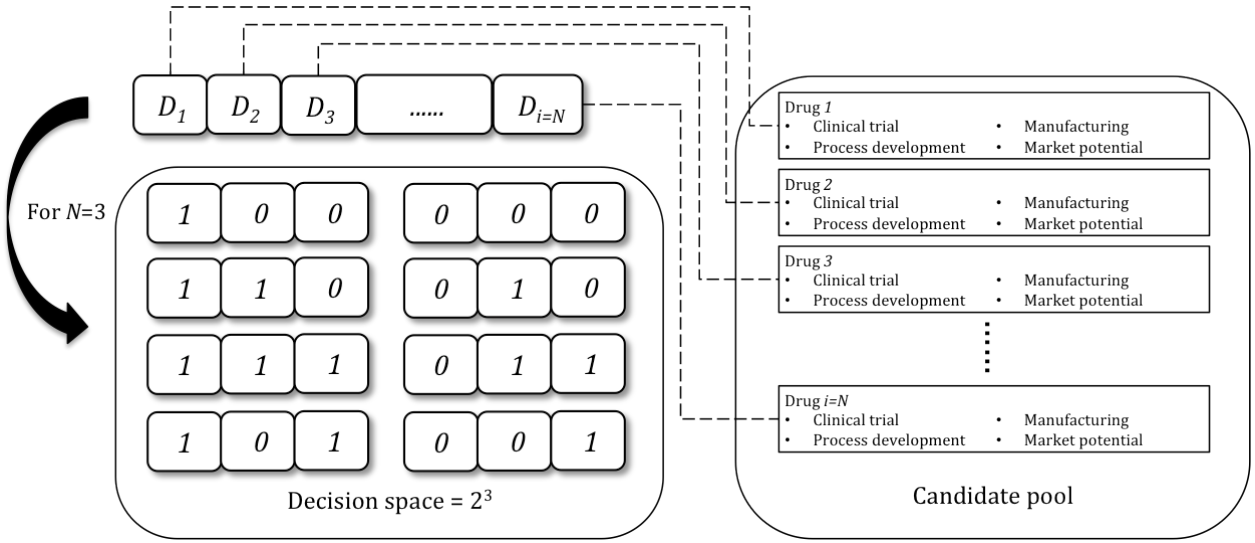


Figure 2.7 A binary string as the solution representing portfolio management decisions.

Each bit represents a product in the candidate pool for selection. The value of the bit indicates the decision of including that product into the drug development portfolio. Changing the value of any one bit from 0 to 1 represents changing the portfolio composition to include the product that this bit represents. For a candidate pool of N products, the decision space is 2^N.

From a performance point of view, the binary string solution structure is the most time-saving in crossover and mutation operations, which can be repeated for thousands of times in running of a genetic algorithm with 100 generations and 100 solutions in the population.

The decision space of portfolio management optimization, in the form of binary string solution structure, is 2^N where N is the number of candidates for selection. Assuming constant time cost for each evaluation, the problem is obviously not polynomial time solvable with any algorithm that is based on traversing through all viable solutions, justifying the use of metaheuristics for more efficient searching of decision space. A medium-size biopharmaceutical company can easily have a 10-product pipeline. For big pharmaceutical companies, their pipeline sizes normally range from 30 to 100 with compounds from various therapeutic areas at different clinical stages. With in-licensing option enabled, the number of eligible product candidates can reach 30 for small and medium biopharmaceutical enterprises and 200 for big pharmaceutical companies. Therefore the maximum decision space for small and medium biopharmaceutical enterprise is around 10^9, for big pharmaceutical companies approximately 10^{60}.

2.4.2 Optimization objectives

Net present value (NPV) is widely accepted as the key criterion for investment decision-making. The methodology of applying NPV rule to decision making is to compare NPVs of all investment strategy alternatives and choose the one that gives the highest NPV. For the purpose of this tool, the investment strategy alternatives are the solutions to biopharmaceutical portfolio development decision-making, which is discussed in the previous subsection.

At the evaluation engine, the tool takes the solution as input and produces the cash flows projections by performing Monte Carlo simulation and dynamic simulation. NPV can be obtained by using the discounted cash flow method:

$$NPV = \sum_{t=0}^{n} \frac{R_t}{(1+i)^t}$$

Where t is the time when cash flow is generated, R_t is the amount of cash flow generated at time t, i is the discount factor, and n is the scope of time range of dynamic simulation. As described before, in the drug development lifecycle cost model, the R&D expenses are viewed as negative cash flow (cash outflow) and the profits from marketing the product are considered positive cash flow (cash inflow). It is possible for NPVs to be negative because the discounted cash outflow may outweigh the discounted cash inflow. In investment terms, the decisions that lead to negative NPVs are considered failure in meeting the pre-determined return on investment.

However, with the integration of Monte Carlo simulation capturing the uncertainties inherent in drug development process, instead of one single NPV, a distribution of NPVs is produced as results of various runs of cash flow projections. Key statistics describing the NPV distribution is adopted as the optimization objectives. They are 1) the average of positive NPVs (APNPV) and 2) the probability of NPVs being positive (p(NPV>0)). The former represents the potential reward should the NPV turn out to be positive, the latter reflects the possibility of this happening.

The rationale behind the selection of optimization objectives is twofold. First, the objectives should provide sufficient information regarding the potential profitability and risk of investment decisions. Using APNPV as the profitability indicator removes the effect of negative NPV and therefore provides a clear picture as to how well the strategy can be on the upside. Meanwhile the value of p(NPV>0) suggests the likelihood of result being on the upside. The second point of selecting these two statistics of NPV distribution is that they are likely to be conflicting in the context of biopharmaceutical portfolio development, given the risk and cost associated with drug development process. Figure 2.8 presents a general categorization of biopharmaceutical portfolio development strategies based on their likely outcomes in these two objectives. The champion strategy triumphs no matter what risk-reward preference the user holds, if such strategy exists.

The gambler's strategy can be competing with the safety strategy as the former focuses on potential reward while the latter suffers mediocre reward in exchange for safety. The selection between these 2 strategy types is entirely dependent on the user preference.

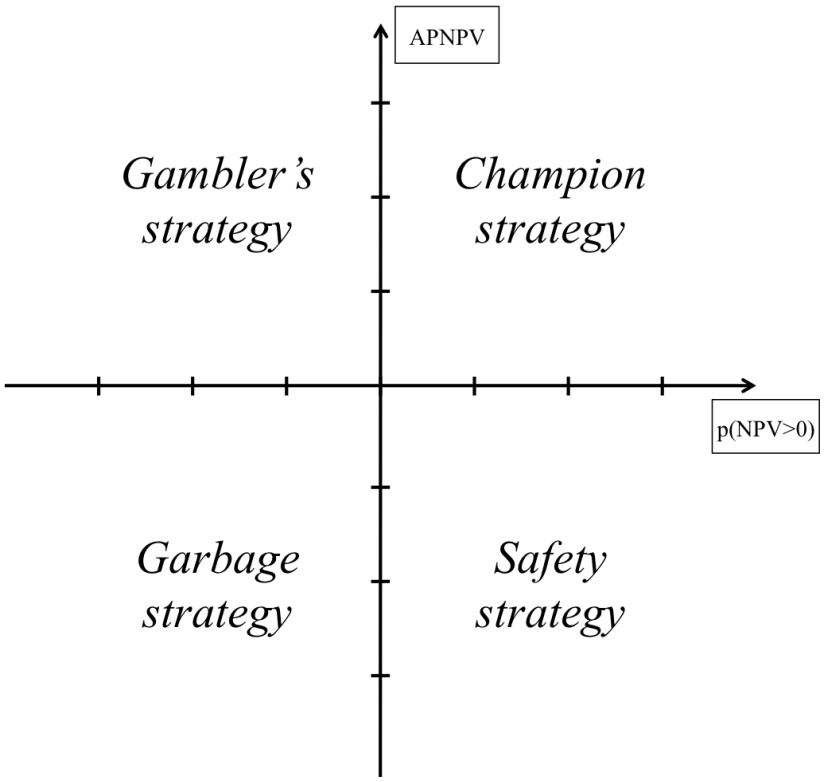


Figure 2.8 The biopharmaceutical portfolio development strategy matrix.

Strategies of portfolio management decisions are categories by 2 key statistics of their respective NPV distributions. The horizontal axis represents the possibility of NPV being positive and the vertical axis represents the average value of positive NPVs.

The Pareto approach is implemented to overcome the difficulties of comparing solutions based on their performances in these 2 objectives. The details of implementation of this approach are described in the next subsection.

2.4.3 NSGA-II

Non-dominated sorting genetic algorithm II (NSGA-II) is a multi-objective evolutionary algorithm that uses non-dominated sorting and crowding distance to differentiate solutions based on their positions in the multi-

objective space. It is very efficient in its fast non-dominated sorting capability to calculate Pareto optimal front and maintaining diversity.

Figure 2.9 presents the essential mechanisms of evolution using NSGA-II. The initial generation of solutions are generated randomly and evaluated to get values of their objectives, APNPV and p(NPV>0). Then a selection procedure performs parental selection by randomly picking two solutions from the initial generation for comparison. The dominating solution from the two is selected as parent solution. The word "dominating" in this context indicates that one solution is strictly better than the other, i.e. it performs better in both objectives. If the two selected solutions are mutually non-dominated, the algorithm randomly chooses one as parent solution. For every pair of parent solutions, the crossover and mutation operators of NSGA-II are implemented, creating two offspring solutions, which are in part the same with their parents. These offspring solutions are then evaluated for performance measure before the algorithm selects another pair of parents for offspring production. This procedure goes on until the number of offspring is the same as the initial generation.

NSGA-II combines the initial population and offspring population as one, and preforms non-dominated sorting, i.e. assign rank to every individual solution by the number of times it is dominated by other solutions. The best solutions are the ones with the least number of getting dominated by other solutions, which is also the one with the lowest number in its rank. The Pareto front is therefore comprised of the solutions that are not dominated by any other solutions, i.e. the solutions with Rank 0.

Within each rank, NSGA-II assigns crowding distance value to every solution. The crowding distance value is higher when solution is more isolated to other solutions in objective space. In this tool with 2 objectives, the crowding distance reaches the highest when solutions are at either end of the Pareto front.

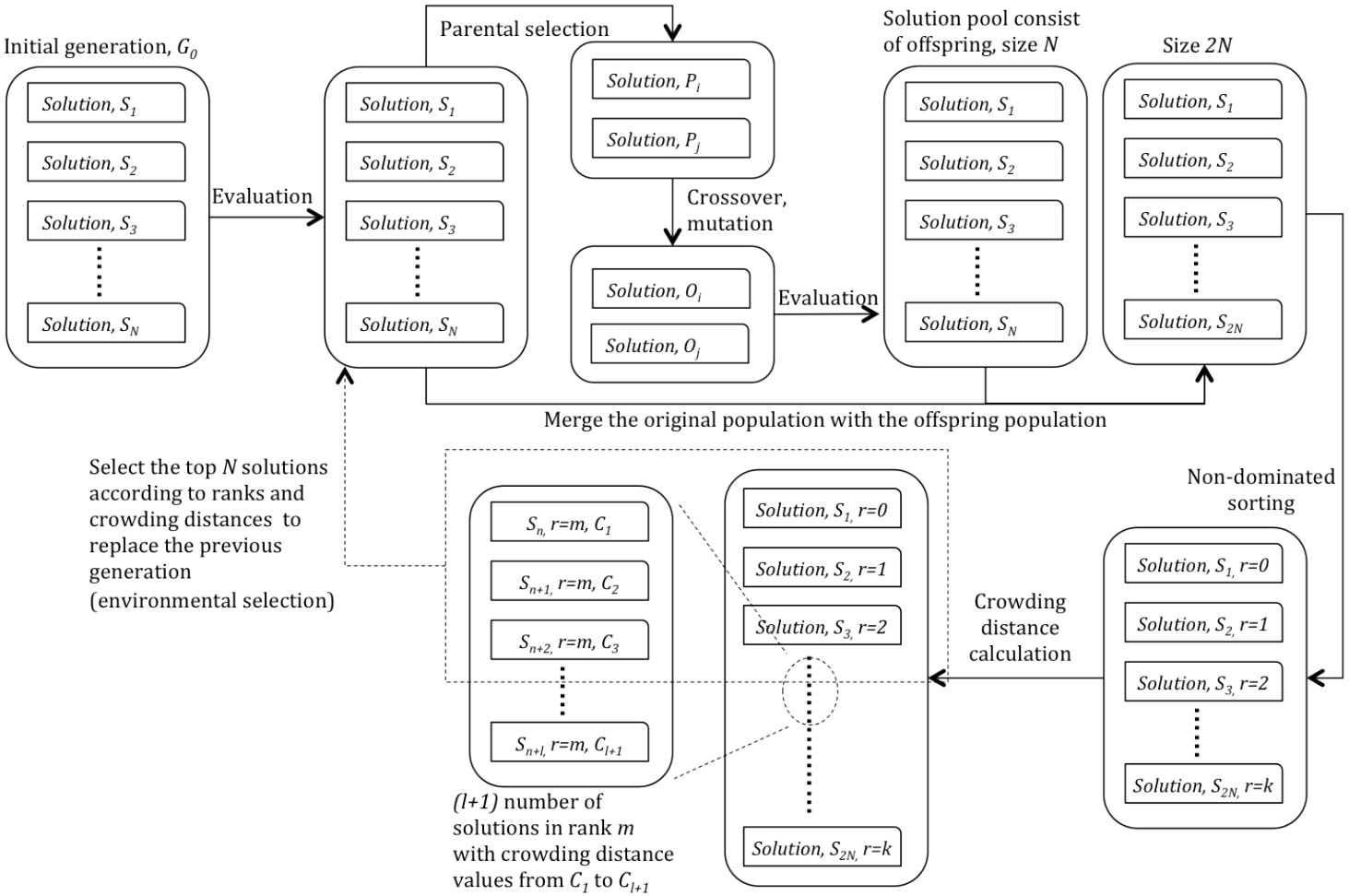


Figure 2.9 Schematic of NSGA-II working process.

This schematic focuses on the generational evolution of NSGA-II, including the parental and environmental selection procedure, the genetic operators, and the non-dominated ranking and crowding distance calculation.

The purpose of non-dominated sorting and crowding distance calculation is to provide support for environmental selection. The environmental selection procedure selects half of the combined population as the next generation based on their ranks and crowding distance values. This procedure first chooses the solutions with the lowest ranks. If the solutions of the same rank cannot be all included in the next generation, the environmental selection chooses the one with higher crowding distance value in order to maintain diversity across Pareto front.

The selected solutions forms the next generation, which will go through the parental selection, offspring generation, evaluation, non-dominated sorting and crowding distance calculation, and finally, like its predecessor, be replaced by environmental selection. The algorithm keeps improving the quality of the population so that the current Pareto front approximates the true Pareto front of the problem.

2.4.4 Managing duplications

Since the initial population is randomly generated and there is no guarantee that the crossover and mutation operators will not create an offspring that is identical to an already generated solution, it is possible that identical solutions exist in the same population. Additionally, the outcome of Monte Carlo simulations for the same solution are not exactly the same, making it possible for identical solutions within the same population being mutually non-dominated. Therefore there can be scenario that after running the algorithm for several generations, the tool ends up with a Pareto front consisting of the same solutions. This scenario is detrimental to the diversity of solutions this tool can provide and should be prevented.

The procedures of preventing duplicated solutions within population is proposed and illustrated in Figure 2.10. These procedures not only prevents solution duplications within population, they significantly improves the quality of evaluation results for solutions that are frequently generated.

To eliminate identical solutions in population, the procedure keeps a record of the current solutions within the population and performs a duplication

check every time an offspring solution is generated. If it is a duplicated solution, the procedure discards the offspring and re-runs the genetic operators to generate a new offspring. However, this is not enough to address the duplication issue across generations. Certain solutions emerge again and again in different generations. The procedure does not discard the results of previous evaluations. It combines them with the new result to make it better.

Table 2.5 presents the equations that can be used to calculate the combined results of evaluations. Based on the equations, the combined results can be calculated when the *k*-th evaluation is finished. The procedure only needs to record 3 variables: 1) the combined results of first (*k-1)*-th evaluations on the average positive NPV, 2) the combined results of first (*k-1)*-th evaluations on the possibility of getting positive NPV, and 3) the number of existing evaluations, *k-1*.

Table 2.5 Equations for updating the evaluation results based on current and previous evaluation results.

Individual evaluation results		Combined evaluation results	
$A_1 = \frac{S_1}{N_1}$	$p_1 = \frac{N_1}{N}$		
$A_2 = \frac{S_2}{N_2}$	$p_2 = \frac{N_2}{N}$	$A_{1\sim2} = \frac{A_1 \cdot p_1 + A_2 \cdot p_2}{p_1 \cdot N + p_2 \cdot N}$	$p_{1\sim2} = \frac{1}{2}(p_1 + p_2)$
$A_3 = \frac{S_3}{N_3}$	$p_3 = \frac{N_3}{N}$	$A_{1\sim3} = \frac{2 \cdot A_{1\sim2} \cdot p_{1\sim2} + A_3 \cdot p_3}{2 \cdot p_{1\sim2} \cdot N + p_3 \cdot N}$	$p_{1\sim3} = \frac{1}{3}(2 \cdot p_{1\sim2} + p_3)$
.....	.....	.....	.....
$A_k = \frac{S_k}{N_k}$	$p_k = \frac{N_k}{N}$	$A_{1\sim k} = \frac{(k-1) \cdot A_{1\sim(k-1)} \cdot p_{1\sim(k-1)} + A_k \cdot p_k}{(k-1) \cdot p_{1\sim(k-1)} \cdot N + p_k \cdot N}$	$p_{1\sim k} = \frac{1}{k}\left[(k-1) \cdot p_{1\sim(k-1)} + p_k\right]$

A_i – average positive NPV for the *i*-th evaluation; p_i – possibility of getting positive NPV for the *i*-th evaluation; S_i – sum of positive NPV for the *i*-th evaluation; N_i – number of positive NPV for the *i*-th evaluation; $A_{1\sim i}$ – average positive NPV for the first *i*-th evaluations; $p_{1\sim i}$ – possibility of getting positive NPV for the first *i*-th evaluations; N – number of Monte Carlo simulations.

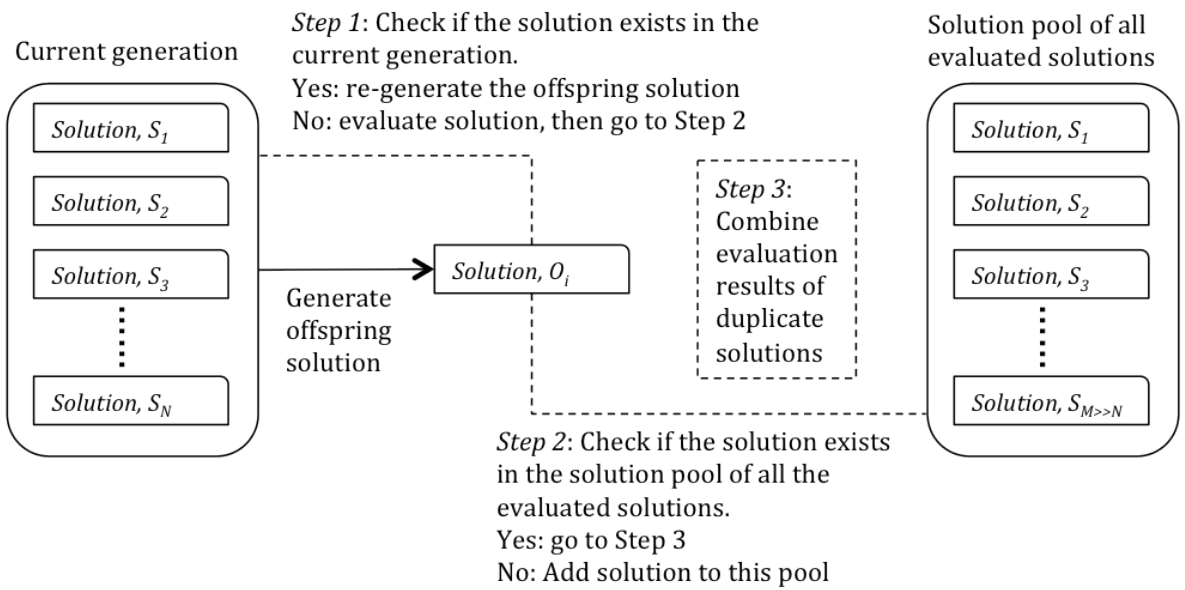


Figure 2.10 Procedures for preventing duplicated solutions within population while improving the quality of evaluation results.

The prevention of duplications within population is achieved through Step 1 by checking if there is identical solutions exists in the population. The purpose of Step 2 and 3 is to combine the results of new evaluation with the results of historical evaluations of the same solution, thus improving the quality of evaluation results.

2.5 DATA MANAGEMENT AND ANALYSIS

In order to effectively collect information regarding the running of optimization algorithm and evaluation of solutions, a system of data reporting formats is designed and implemented. The information is initially recorded in Java using custom designed variables such as multi-dimensional arrays. A data output class responsible for printing results into text document is created to transfer information from those variables to outside text files.

There are 3 major types of reports. The generational performance report presents the information collected during the running of the optimization algorithm concerning the overall performance of solutions for a given population. These reports are placed in a generation-specific folder, along with folders for solutions and reports that are related to this generation. Table 2.6 presents the data-reporting format of the generational performance report with sample data. The purpose of this report is to record the performance information about a solution and its decision variables. Analysis of optimization results from decision space and objective space is based on this report.

Table 2.6 Format of generational performance report.

Index	Rank	APNPV	p(NPV>0)	D_1	D_2	D_3	D_4	……
1	0	15324789	0.54	0	1	0	0	……
2	0	13365987	0.56	0	1	1	0	……
3	1	12568712	0.49	1	0	0	1	……
……	……	……	……	……				

Note: The report gives an index for each solution and presents the values of its objectives, the decision variables, and the non-dominated ranking.

The cash flow report records the timing and origin of cash flows as well as their amounts for a given Monte Carlo simulation. The number of cash flow reports within a solution folder equals the number of Monte Carlo

simulations. Table 2.7 describes the format of cash flow report for a given Monte Carlo simulation. A multi-dimensional array was designed to accommodate the production of cash flow reports. At the start of each Monte Carlo simulation, this array is initiated with $t \cdot s \cdot 3$ dimensions where *t* represents the number of time slices for dynamic simulation, *s* represents the number of stages in the drug development lifecycle, and 3 represents the 3 types of activities this tool simulates, namely the clinical trial, manufacturing, and process development. In the end of this Monte Carlo simulation, a method is called in the data output class to transform the multi-dimensional data into a text file in Table 2.7 format.

Table 2.7 Format of cash flow report. The report specifies the timing, origin, and stage for each cash flow.

Time	Stage	Type	Value
1	Phase I	Clinical trial	-35
1	Phase I	Process development	-12
1	Phase I	Manufacturing	-10
2	Phase I	Clinical trial	-35
2	Phase I	Process development	-12
……	……	……	……
123	Phase III	Clinical trial	-72
123	Phase III	Process development	-20
123	Phase III	Manufacturing	-22
……	……	……	……

Along with the production of a cash flow report, an activity report is generated for each Monte Carlo simulation. This report presents the actual timings of activities that are triggered and their states on completion. Table 2.8 presents a sample activity report. The activity report provides critical information in the analysis of delays and project failures.

Table 2.8 Format of activity report.

Product	Stage	Type	Start time	End time	State
Drug 1	Phase II	Clinical trial	289	372	Pass
Drug 1	Phase III	Clinical trial	381	503	Fail
Drug 1	Phase III	Manufacturing	360	380	Pass
Drug 1	FDA	Process development	450	503	Interrupted
……	……	……	……	……	……
Drug 2	Phase I	Clinical trial	112	173	Pass
Drug 2	Phase II	Clinical trial	173	297	Pass
Drug 2	Phase II	Manufacturing	158	170	Pass
……	……	……	……	……	……

Note: This report reveals the timing of triggered activities and their states on completion of 1 Monte Carlo simulation.

The analysis and visualisation of data in the above report formats were accomplished using R statistical computing language with ggplot2 data visualization package. The application can be found in Chapter 4 where the stochastic optimization tool is implemented. For results generated from drug development lifecycle cost model for cost evaluation purpose, Excel charts were created for data visualization in Chapters 3 and 5.

2.6 CONCLUSION

In this chapter, an activity-based drug development lifecycle cost model is proposed to capture the clinical and non-clinical aspects of biopharmaceutical portfolio development. The model is further developed with Monte Carlo simulation capability and dynamic simulation mechanisms, so that it functions as an evaluation engine for support of portfolio management decision-making under uncertainties and resource constraints. This evaluation engine produces performance appraisals for portfolio management strategies in the form of NPV distributions.

A multi-objective evolutionary algorithm NSGA-II is implemented in the stochastic optimization tool in order to efficiently search the decision space for optimal solutions. A binary string representation of portfolio management decisions is proposed for improved flexibility under changing portfolio development environment, and efficiency in genetic operations during the running of the algorithm. The algorithm makes use of Pareto optimal approach in dealing with competing optimization objectives, i.e. the two key statistics of the NPV distribution, the average positive NPV (APNPV) and the possibility of NPV being positive (p(NPV>0)). A procedure of managing solution duplications in population and in the course of optimization is introduced to maintain diversity and improve the quality of evaluations of frequently generated solutions.

Various data reporting formats are introduced to facilitate the analysis of cost evaluation and portfolio management optimization results. The data management system takes advantage of the object-oriented, activity-based drug development cost model and stochastic optimization tool to produce reports that reflect the performance of generations, the cash flows and their respective origins, and the details of simulation of activities in their most explicit form. Excel charts and R statistical computing language are adopted in visualizing the results.

Application of the drug development lifecycle cost model is presented in Chapter 3 to benchmark the cost of clinical and non-clinical activities for pharmaceutical and biopharmaceutical portfolio development. The model is further implemented in Chapter 5 with application to cost evaluation of cell therapy portfolio development. The stochastic optimization tool for biopharmaceutical portfolio management decision support is implemented in Chapter 4 with custom designed candidate pool featuring products of various risk-reward characteristics.

CHAPTER 3

COST OF MANUFACTURING AND PROCESS DEVELOPMENT IN BIOPHARMACEUTICAL NEW PRODUCT DEVELOPMENT

3.1 INTRODUCTION

The pharmaceutical industry has suffered from diminishing R&D productivity and increasing R&D cost over the past decade (Scannell et al. 2012). Typical portfolio return on investment often falls short in recovering the capitalized cost of development considering the complexity and risky nature of developing new therapeutics. Compared to conventional pharmaceutical small molecule NMEs, biological products have a relatively higher overall success rate. Probabilities of FDA approval for investigational drugs in Phase I have been estimated to be 7.5% for NMEs and 14.6% for biologics (Hay et al. 2014). However, biological products are exposed to more technical difficulties in process development and manufacturing. Constant improvement of production methods requires the assessment of comparability to ensure the consistency of product characteristics that could affect safety, purity, efficacy, and stability of the finished product. Published studies have focused on evaluating the overall cost of R&D, but have not addressed the clinical and non-clinical cost breakdowns at each phase. Using the model proposed in the previous chapter, this chapter aims at benchmarking the costs across the drug development lifecycle with special attention to the non-clinical activities, i.e. process development and manufacturing.

Pre-clinical and clinical trials often lie on the critical path of biopharmaceutical product development, with support from process development and manufacturing. Provisional budget allocations and planning are required to safeguard the smooth running of R&D activities. Therefore there is a need to accurately estimate the cost of process development and manufacturing activities for different attrition rate scenarios. On the manufacturing level, published cost of goods analyses (e.g. Simiaria et al. (2012); Pollock et al. (2013) were drawn upon in this study to

determine and benchmark the manufacturing costs for the portfolio at each development stage for different attrition rate configurations. Estimations of personnel required in process development activities across developments stages are discussed and utilised as the basis for process development cost evaluation.

A pharmaceutical product development pathway model is introduced to address the cost of non-clinical activities in the context of portfolio development targeting one market success. The general idea of capturing the "at-risk" nature of process development and manufacturing activities in portfolio development was developed and described in Chapter 2. In this chapter, the model is applied to a case study featuring industrially relevant drug development risk and cost scenarios. The model is further extended by an analysis of cost associated with the "at-risk" characteristics of non-clinical activities in probabilistic scenarios.

The remainder of this chapter is structured as follows. In Section 3.2 and Section 3.3 the model of drug development lifecycle, as well as its structure, is described. Section 3.4 explains the assumptions made for capturing the impact of delays in process development activities. The background to the case study is described in Section 3.5, which benchmarks attrition rates, costs, and timeline of milestones for single product development. Cost evaluation of portfolio development and the analysis of economic implications of delay are discussed in Section 3.6.

3.2 DRUG DEVELOPMENT LIFECYCLE DESCRIPTION

The biopharmaceutical new product development process follows an established pattern. An exploratory discovery research finds a new target of potential therapeutic use, then a number of molecules are developed and optimized, and the best one among them is selected to be the product candidate. This product candidate then goes through the pre-clinical trial phase where a range of tests are run both in vitro and in animals to characterize the likely safety and effectiveness of this molecule in treating

its target disease. Upon completion of the pre-clinical trial, the drug developer applies to regulatory authorities (e.g. FDA in USA) for approval to commence human clinical trials. Clinical trials are required to prove that the drug is safe and effective when administered to human patients. There are three major phases of clinical trials before the product gets approval for commercialization: Phase I tests the safety of the product in human, Phase II assesses its efficacy and Phase III aims at definitively assessing the efficacy and dosage in a large number of patients. Upon completion of clinical trials, the drug developer is required to gather all pre-clinical and clinical data generated during the process, along with details of the production process used to make the drug and cGMP documentation, and submit to the regulatory authority for market entry approval. Once granted, the product developer can legally manufacture and sell the product.

This study focuses on the development stages from pre-clinical to regulatory submission (i.e. the FDA review). The activities prior to the pre-clinical trial stage are not covered in this model because the costs generated at these stages are often shared with other compounds. Therefore the stages from discovery to lead optimization are omitted, leaving pre-clinical and clinical trial stages as the major cost drivers in this model.

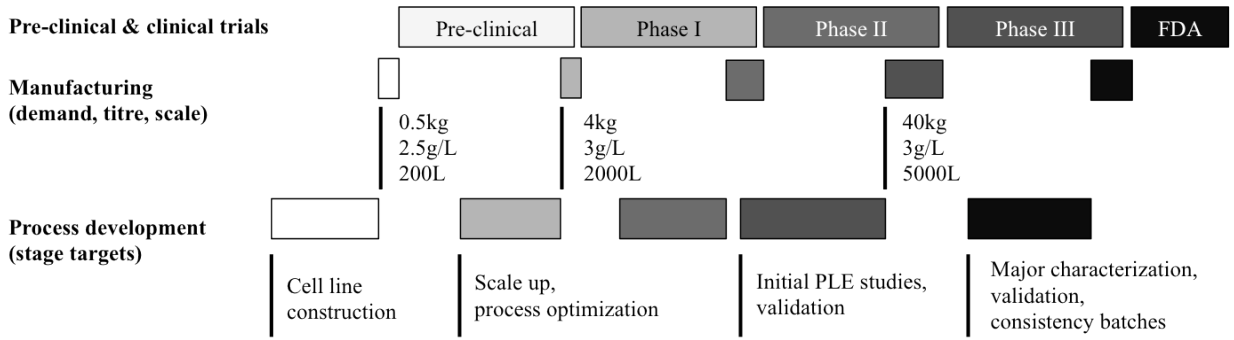
The development pathway described in this study assumed that only the pre-clinical and clinical trials are on the critical path. To meet the timing requirement of activities on the critical path, the supporting process development and manufacturing activities occur off the critical path and hence are performed at risk before the go/no-go decision for the clinical trial is known. This model assumes for every development stage, the dependency exists that the occurrence of activities follows the path from process development to manufacturing, and then to the clinical trial.

Manufacturing and process development activities are designed to meet the need of the clinical trials. In order to produce the products efficiently and at the required quality, the developer must, through a serious of process development activities, establish the manufacturing process and optimize it

to meet regulatory requirements as well as reduce cost. Detailed inter-dependencies between clinical trial, manufacturing and process development activities are depicted in Figure 3.1. Pre-clinical trial materials are produced through an established cell line that provides products with low titre at a small scale. For Phase I and II clinical trials, process development focuses on process scalability and improvement of productivity, since more material is required for clinical trials. Process development for Phase III and regulatory approval mainly focuses on process characterization and validation. Initial process limit evaluation and validation studies commence at the early stage of process development prior to Phase III. Major characterization and validation studies run simultaneously with Phase III clinical trials in order to avoid causing any delay to submission to regulatory approval. Typical values of manufacturing scale and titre are incorporated in this model as 200L and 2.5g/L for pre-clinical, 2000L and 3g/L for Phase I and II, and 5000L with 3g/L for Phase III and consistency batches required to validate the process. The Phase III scale of production was selected to match a typical commercial scale of production of 200kg/y for mAbs (Kelley 2009), which can be achieved with 20 batches at the 5000L scale and 3 g/L titre. The scale and titre of manufacturing for commercialization is usually kept the same as Phase III, but this is not included in this study as it focuses on the costs of new product development.

Figure 3.1 Dependencies between process development, manufacturing, and clinical trials.

The process development activities first establish manufacturing procedure to produce material in small scale and low titre in order to supply for pre-clinical and early phase clinical trials. Then as the development of the product proceeds larger quantity of material are required for clinical and commercialization demand, hence the need for scale-up the size of production and optimize the titre and yield. Late stage process development also focus on regulatory compliance. The process parameters need to be characterized and process consistency validated before submission to regulatory approval.



3.3 DRUG DEVELOPMENT LIFECYCLE COST MODEL STRUCTURE

A spreadsheet-based lifecycle cost model was built for biopharmaceutical drug development that captured the costs, durations, risks and interdependencies of both the clinical and non-clinical activities. The non-clinical activities were broken down into process development and manufacturing. The term 'process development' was taken to include all bulk process and formulation development as well as the analytical effort for process characterisation and validation studies. The term 'manufacturing' was taken to include the cost of manufacturing batches for supply of material to pre-clinical and clinical trials as well as process validation/qualification consistency batches required for BLA submissions. These manufacturing costs were determined using a bioprocess economics model developed at UCL (Simaria et al. 2012).

The tool establishes the product development pathway with the number of projects necessary to achieve a certain pre-set target. The evaluation of out-of-pocket costs along the development pathway for a given year is based on two criteria: number of projects in the pipeline and total out-of pocket cost of a single project in that year.

Figure 3.2 lists the required input parameters for the model and the processed costs in pipeline and project-specific levels. On the pipeline level, the model requires the user to define their target in the form of desired number of successful market entries, and the cost of capital in the form of discount rate. Project profitability is defined as the sales curve of the product that goes to market once the project is successful. Availability of technology platforms for process development activities is also considered on the project-specific level in this model. For pre-clinical and clinical studies, the phase transition probabilities (TP) are required to calculate the required number of projects to achieve the user's desired target; duration & cost provides the basis for cost distribution in time; and demand of materials at clinical trial stages provides guidance on manufacturing cost evaluation.

Batch scale and batch cost are inputs provided at the manufacturing level to determine the number of production batches and the related cost. Finally, the cost and duration of process development activities are required, as well as the risk of delay in probabilistic form.

The model then converts the inputs into outputs. At the beginning of the evaluation, the model builds up the timeline of the development pathway according to the inputs on duration of pre-clinical and clinical trials. Then based on their material requirements, the model generates manufacturing activities with the appropriate number of production batches. The timings of manufacturing activities are set to meet the clinical material requirement. The process development activities are planned to provide technical support for manufacturing at various stages. After the model plans all the clinical and non-clinical activities for developing a single product, it starts to calculate, based on the attrition rates of the development cycle, how many products the user needs at each step to achieve the target number of market successes. With the number of products being developed and the cost of developing each one determined, the total cost is evaluated.

The outputs at the pipeline level provide the user with information concerning how much it costs to achieve their target in terms of total capitalized cost. Figures on the out-of-pocket costs for each year are also presented as outputs and they serve a more practical purpose for budget planning. More specifically, the cost breakdown of clinical trials, manufacturing and process development is also available for more detailed budget planning. On the project level, the model produces the costs of each individual project and the time of proposed market entry, which gives the decision maker an indication of the amount of investment and the time to market. In addition, the model also provides valuations of a single project by development stage, which could be more useful to parties involved in product licensing deals.

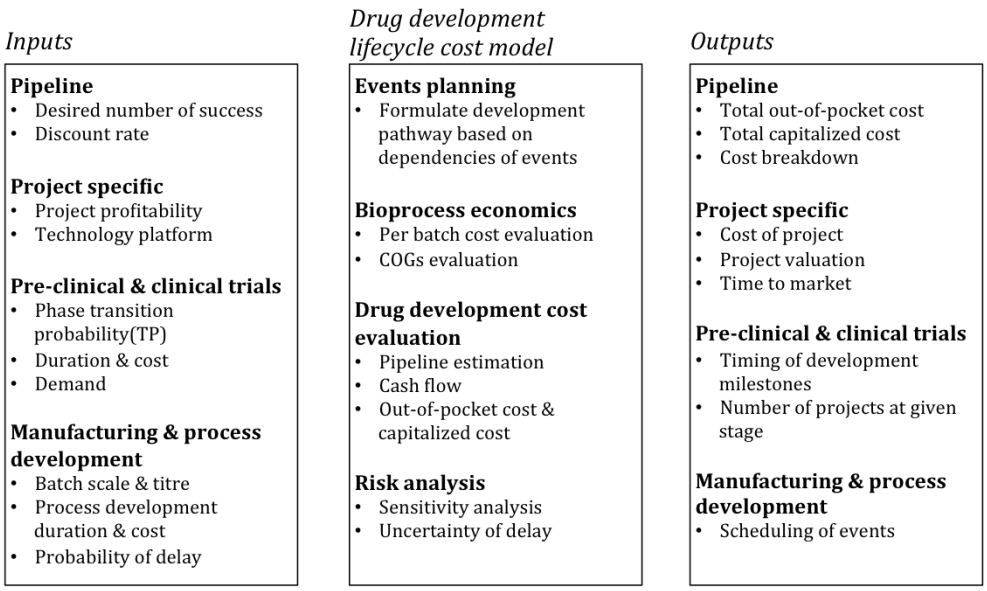


Figure 3.2 Tool structure with input and output parameters for the model.

The flow of information is from the left side of inputs, through the drug development lifecycle cost model in the middle for calculations, to the outputs of results in various formats on the right side.

3.4 ADDRESSING THE RISK OF DELAY

This tool is capable of analysing cost when the risk of development delay is considered. The starting and end times of development activities are results of scheduling without leaving margin for possible delays. Therefore whenever a delay occurs during a certain development activity, the timing of the subsequent dependent activities are affected and eventually delays the product's marketing approval. From the out-of-pocket cost perspective, this model assumes that the rate of spending is constant over time for each activity, so the delayed activities cost more. From the capitalized cost perspective, it costs more when the spending period is prolonged. More importantly, a delay in market entry could be detrimental to a product's sales, causing it to lose value.

Delays of development activities are modelled in a probabilistic fashion in this model. Every activity has a probability of delay and two possible outcomes: normal and delayed. In this way, a binary tree, given the chance

and impact of delay for all activities, can be used to describe every possible scenario of biopharmaceutical new product development pathway when risk of delay is considered. The tool evaluates the cost structure for every possible scenario and calculates the expected values of cost using the probabilities of these scenarios.

3.5 CASE STUDY SETUP

The purpose of this set-up is to simulate the process of biopharmaceutical new product development pathway so that the process development and manufacturing costs across the biopharmaceutical drug development cycle can be estimated. Hence it was critical to have representative input values for the key risks, costs and timelines in the development cycle. The key assumptions were derived through a detailed review and comparison of various sources of industrial cost analysis data so as to derive representative figures as inputs for this study. An established manufacturing process economics model (Simaria et al. 2012) was utilized to derive the manufacturing costs at different titres and scales of production.

3.5.1 Development risk profiles

The clinical failure rates at each phase in the drug development process play key roles in cost evaluation. In this model, the risk of clinical failure is characterized by the phase transition probabilities (TPs) of projects. Published statistical data were drawn upon when building up the case study scenarios, as presented in Table 3.1. The first scenario features the most optimistic situation where the highest phase transition probabilities published for each stage were used (DiMasi & Grabowski 2007; Bogdan & Villiger 2010; Paul et al. 2010). Scenario 2 used an industrial average for the phase transition probabilities derived from Paul et al. (2010) to provide a more balanced evaluation. Scenario 3 represented a more pessimistic outlook. It used the industrial average phase transition probabilities from pre-clinical to Phase II stage, but addressed the possibility that for some

therapeutic areas such as Alzheimer's disease, the phase transition probability of Phase III could be extremely low due to the novelty of the drug targets being pursued and to the lack of animal models with a strong capacity to predict human efficacy (Pauls et al. 2010). The likelihood of approval (LOA) and the required numbers of products for one market success from Phase I to market approval for all 3 scenarios are also presented.

Table 3.1 Risk profiles of new biopharmaceutical product development represented by phase transition probabilities.

Phases	PC	I	II	III	FDA	PhI LOA[a]	PhI N[b]
Optimistic	70%	85%	55%	70%	91%	29.8%	3.4
Average	69%	54%	34%	70%	91%	11.7%	8.6
Pessimistic	69%	54%	34%	21%	91%	3.5%	28.5

[a] LOA = likelihood of approval from Phase I.

[b] N= number of Phase I products required for one market success.

3.5.2 Cost estimations for developing a single product

Cost of process development

The definitions of process development and its associated costs in biopharmaceutical product development vary between sources and orgnaisations. In this model, process development was defined as the activity that establishes and optimizes the manufacturing of biopharmaceutical product for clinical and commercial purposes, and provides knowledge for regulatory compliance. The cost associated with process development was therefore distributed across strain development, process synthesis, design, optimization, characterization, validation, and the related analytical development activities. The cost of manufacturing clinical material was not included in the cost of process development, regardless of its scale. The cost of manufacturing consistency batches for process validation purpose was included in the cost of process development, only if

the product was not used in clinical trials or commercial sales. Otherwise it was considered as a cost of manufacturing. This case study assumed that the material produced from consistency batches would be used for Phase III clinical trials, therefore the related manufacturing cost was not included in process development.

The estimation of process development costs adopted a full-time equivalent or FTE year based approach. This approach first reviewed the necessary tasks for each step of process development in biopharmaceutical new product development, then derived the workload required to fulfil these tasks in terms of FTE year, and applied a fixed cost incurred to the company in every unit of FTE year to account for the actual cost of process development.

Table 3.2 contains the estimated FTE required for major process development activities in this model. The calculation of FTE was based on the number of personnel and their relative involvement in performing their function compared to a full-time employee. As an example of calculation, an employee working 2 hours per working day on this project only accounted for 0.25 FTE. This principle applies to all the personnel working in regulatory support and QC/QA functions that are not dedicated to any specific project.

The cost of the process development activity was determined based on the total workload it required. On average, for every unit of FTE year workload, the overheaded cost incurred to the company was assumed to be $250,000, including not only the FTE salary, but also all accompanying cost in process development.

Table 3.2 Estimated personnel and cost for process development activities in new biopharmaceutical product development (J. Coffman, Boehringer Ingelheim, personal communication).

Stages	PC/Phase I	Phase II	Phase III	FDA (PD)	FDA (Comm)
FTEs					
Project manager	1	1	2	2	0
Process scientists	3	6	10	12	0
Tech-transfer	1	2	4	4	0
Regulatory support	0.5	1	2	10	0
QC/QA	0.5	2	2	4	20
Site support	0	0	0	0	20
Total FTE	6	12	20	32	40
Duration (year)	1	0.5	2	1.5	1.5
FTE year	6	6	40	48	60
Cost ($ million)	1.5	1.5	10	12	15

Note: The process development activity in FDA review stage is divided into 2 separate parts: FDA (PD), with the original process development team working towards submission, and FDA (Comm) with a team of QC/QA and site support personnel working on commercial manufacturing.

For every step of process development, it was assumed that a project manager was required to work full time in order to coordinate the work of the team and communicate with other relevant divisions of the company that facilitate the on-going process development. For the early stages of development, one project manager was assumed to be sufficient for the relatively small process development team, whereas for the late stages of development, the size of the team increases significantly so that one extra project manager was required. Process scientists are needed for upstream and downstream process establishment, optimization, characterization, and validation. Hence they are needed from the start of the development life cycle. Requirement of personnel in charge of tech-transfer to pilot and large-scale manufacturing increases as the scale of manufacturing increases.

The FTE required at a scale of 200L, 2000L, and 5000L was set as 1, 2, and 4, respectively. The regulatory support required at pre-clinical and clinical stages is much less than that required at the FDA review stage. The QC/QA personnel works on developing analytical assays for process development, but they are normally working for multiple projects. The FTE figures for QC/QA were adjusted by the number of projects that one specialist can simultaneously handle and the number of specialists required for each process development step. The process development activities at FDA review stage were divided into two areas, with the original process development group working on the final process characterization, validation, and documentation for submission, while another group consisted of QC/QA and site support personnel working on preparations for commercial manufacturing. Given the definition of process development described earlier, the preparation of commercial manufacturing was considered as part of process development, and hence it was important to include the cost incurred.

Cost of manufacturing

The cost of manufacturing in pre-clinical and clinical development was calculated using an established UCL process economics model (Simaria et al. 2012) with inputs on scale of fermentation, titre, and clinical material demand. Estimation of material demand in clinical trials was based on the number of patients participating in each stage. Table 3.3 presents the assumptions for patient numbers for clinical trials. With the assumptions that the average patient body weight is 86kg and the approximate dosage per body weight is 7mg/kg, one dose of treatment requires 0.602g material. For Phase I, 1 dose per patient is sufficient to test product safety. For Phase II and III, the number of doses administered per patient is related to the length of test period and the frequency of administration. This case study assumed the frequency of taking 1 dose every 2 weeks and the average lengths of clinical test for Phase II and III were 0.5 and 1 year, respectively. Typically, drug developers produce more product than needed for clinical trials to

support non-clinical uses related to quality analysis and testing as well as contingency inventory(e.g. in case of change in dosage or product loss). The ratio of overproduction applied to early phases is 250% and for Phase III is 125%, as the uncertainty of manufacturing decreases. The adjusted demand that takes into account the overproduction was therefore considered the target demand for the process economics model to calculate the manufacturing cost. The target demand of pre-clinical stage material was assumed 0.5 kg, according to industrial opinion (J. Coffmann, Boehringer Ingelheim, personal communication).

Table 3.3 Estimation of bulk product demand in clinical trials.

Stage	Patient number[a]	Duration (year)	Dose	Demand	Over production	Adjusted demand
Phase I	40	n/a	40	24 g	250%	4 kg
Phase II	200	0.5	2600	1.6 kg		
Phase III	2000	1	52000	31.3 kg	125%	40 kg

[a] The estimated patient numbers are from previous modelling research (Simaria et al. 2012)

The adjusted demands for pre-clinical and clinical trials were then fed into the process economics model for calculation of the manufacturing cost. Assumptions related to the fermentation scale and titre are presented in Table 3.4. At the pre-clinical stage, the manufacturing process is established at a pilot scale of 200L and the titre 2.5g/L. At Phase I and II, 2000L cGMP facility with 3g/L titre was assumed to be the standard set up of manufacturing. The fermentation scale was further increased to 5000L and titre maintained at 3g/L at Phase III, as more material was required at this stage and this process scale would be locked for commercialization. The improvement of manufacturing scale and titre was considered the result of process development.

The process economics model determined the cost per batch and this was split into two categories: direct and indirect cost. The direct cost accounts

for the use of labor, consumables, chemical reagents, and direct utilities during the manufacturing process. The indirect cost accounts for the cost of running the facility, including maintenance, general utilities, and capital charges. The indirect cost per batch was determined by spreading the annual indirect cost over a representative number of annual batches (20 in the pre-clinical facility) and 10 in the clinical facilities).

Table 3.4 Estimation of batch cost and number of batches required in new product development.

	Model inputs			Cost per batch ($ million)			
	Scale (L)	Titre (g/L)	Demand (kg)	Direct	Indirect	Total	Batch required
PC	200	2.5	0.5	0.25	0.12	0.37	3
Ph I & II	2000	3	4	0.56	0.71	1.27	2
Ph III	5000	3	40	0.91	0.89	1.8	5[a]

The direct cost per batch includes cost from labour, consumables, chemical reagents, and direct utilities. For the labour cost, the model assumes 4 operators working in the pre-clinical pilot scale facility and 9 operators working in larger scale facilities. The indirect cost accounts for the cost of facility maintenance, general utilities, and capital charges. These items are linked to the cost of fixed capital investment of building the facility. The Lang factor of facility supplying for pre-clinical, Phase I &II, and Phase III is 4.5, 6, 6 respectively. Using 4.5 as Lang factor for pre-clinical facility because GMP is not required. The indirect cost generated by having the facility is calculated as an annual average. The indirect cost per batch is calculated by spreading the annual indirect cost evenly to the number of batches produced. The number of batches produced every year at pre-clinical facility is 20; at clinical facility is 10.

[a] 3 of theses Phase III batches are also used for consistency batches.

Cost of clinical trials

Clinical trials contribute most to the total cost of developing biopharmaceutical new products. Various sources have published stage costs of developing new products, which can be considered as the total costs of clinical trials, manufacturing, and process development. Therefore, this model derived the costs of clinical trials using published total cost excluding

the non-clinical components, namely the process development and manufacturing costs described in the previous sections. As shown in Table 3.5, the cost of clinical trials were derived by deducting the non-clinical costs from published total stage costs. For pre-clinical trials, the $7 million total stage cost from Bogdan & Villiger (2010) was adopted as DiMasi & Grabowski's (2007) figure includes costs from previous stages. For FDA review stage cost, the published figure refers to pharmaceutical industry in general, not specific to biopharmaceuticals. Hence the cost of clinical trial only accounts for the fees required for BLA license.

Table 3.5 Assumption on cost structures and comparison to published total stage costs for biopharmaceutical new product development.

Cost ($ million)	Pre-clinical	Phase I	Phase II	Phase III	FDA
Published total					
DiMasi & Grabowski 2007	59.88	32.28	37.69	96.09	N/A
Paul et al. 2010	5	15	40	150	40
Model assumptions					
Process development	1.5	0	1.5	10	27
Manufacturing	1.11	1.27	1.27	9[c]	0
Clinical trials (DiMasi)	4.4[a]	31	35	77	3[b]
Clinical trials (Paul)	4.4	13.7	37.2	131	3

[a] Cost of pre-clinical clinical trial is calculated based on $7 million stage cost (Bogdan & Villiger 2010).

[b] $3 million is license cost only at FDA review stage.

[c] This cost includes the cost to produce consistency batches.

3.5.3 Development timeline and milestones

To establish the new product development pathway, durations of activities and their dependencies are required. Table 3.6 presents the durations of activities from 3 categories, based on published sources and industrial opinion. Zero duration of activities indicates that there is no activity from

the category at the given development stage. Therefore from Table 3.6 it can be seen that it was assumed there would be no process development for the Phase I stage as the process would not be changed typically between animal and the first-in-human trials, and no manufacturing activity for clinical trials at FDA review stage.

Table 3.6 Duration of activities.

Stage	PC	I	II	III	FDA
Clinical trial duration (year)	1	1.6	2.4	2.7	1.5
Process development duration (year)	1	0	0.5	2	1.5
Manufacturing duration (week)	6	5	5	13	0

Note: Durations of clinical trials are from DiMasi & Grabowski (2007); duration of pre-clinical is from Paul et al. (2010); durations of process development and manufacturing are from industrial expertise (J. Coffman, Boehringer Ingelheim, personal communication), given the task for process development and number of production batches.

In this model, the dependencies between these 3 categories of activities follow the rationale that 1) clinical trials, including pre-clinical tests, require clinical material supply which is the result of manufacturing activities; 2) manufacturing is supported by process development. So for any given development stage, the order of activities is from process development to manufacturing, and then to clinical trials, unless there is no such activity at that stage. Due to this set up, some activities have to run at risk of project failure, as depicted in Figure 3.3. This includes the manufacturing of Phase I and II materials, and the process development for Phase II. For Phase III, only part of the process development activity is running at risk because there is a preparation stage between the decision to continue and the actual clinical material demand.

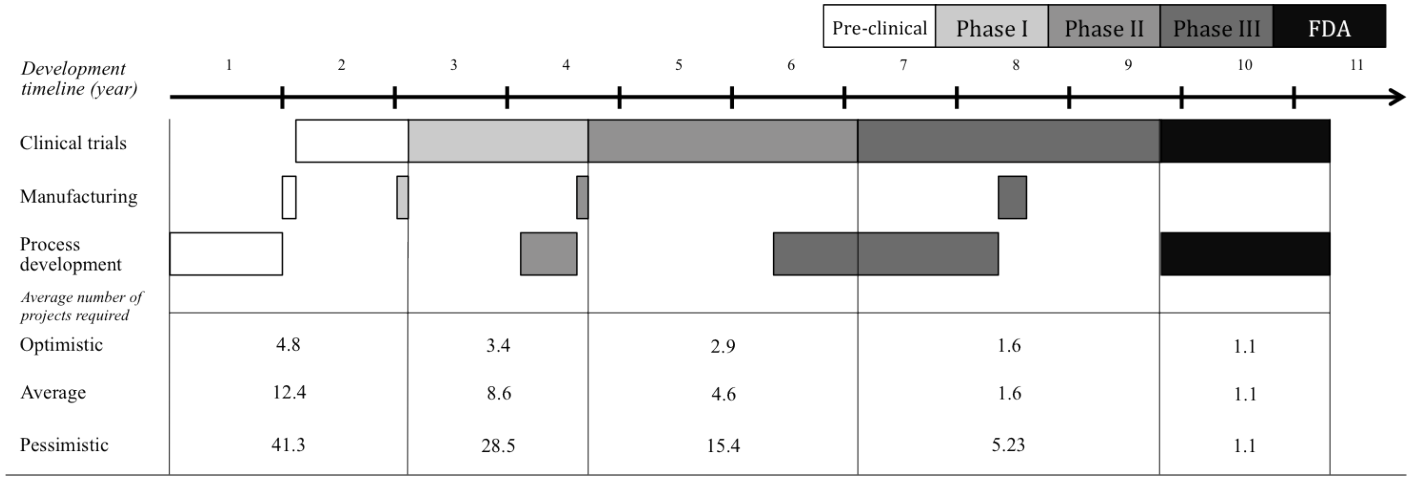


Figure 3.3 Timeline of new biopharmaceutical development activities separated by milestones.

The degree of grey represents the advances of development stages towards market entry. The average numbers of projects required to achieve one market success at each stage were calculated from the phase transition probabilities from 3 scenarios featuring optimistic, average, and pessimistic assumptions for the product risk profiles. Because of the lengthy duration for patient recruitment, the actual need for clinical trial material in Phase III does not appear until 1.5 years after the success of Phase II

3.6 RESULTS AND DISCUSSION

A detailed analysis is presented of the process development and manufacturing costs across the biopharmaceutical drug development cycle. The non-clinical budgets needed at each phase of development to ensure a market success each year were estimated. The impact of different clinical success rate profiles on the process development and manufacturing costs at each stage was investigated.

3.6.1 Cost evaluations

The initial results were generated by the model to benchmark cost, time and number of projects that would finally achieve one market success at the end of development pathway. Under the given case study set-up, the model constructed a full R&D portfolio with the number of projects required to achieve the desired target. The development pathway was established for each project and its corresponding manufacturing and process development activities scheduled. The costs along the development timeline are calculated for 3 scenarios.

The total out-of-pocket cost to have one market success was calculated by the model to be $442 million, $748 million, and $2417 million for 3 scenarios featuring low, average, and high risk of failure in the process. The percentage of a biologics company's R&D out-of-pocket costs that needs to be allocated to process development and manufacturing for each biopharmaceutical launched was found to vary between 16.8-21% for Phase I to launch success rates of 3.5 - 29.5%.. This translated into total manufacturing out-of-pocket costs for the portfolios under the three risk profiles of $30M, $54M, and $182M respectively and total process development out-of-pocket costs of $62M, $88M, and $225M respectively. Figure 3.4 indicates the breakdown of the portfolio costs for the industrial average scenario. The results indicate how process development and manufacturing budgets should be distributed across the various phases. In

Figure 3.4, in terms of non-clinical activities, the Phase III process development and manufacturing consumes the highest proportion of out-of-pocket funds per success ($41M in the industrial average case), followed by the non-clinical cost for preclinical stage ($32M), process validation/characterization in the FDA review stage ($30M), Phase II ($24M), and then Phase I ($16M).

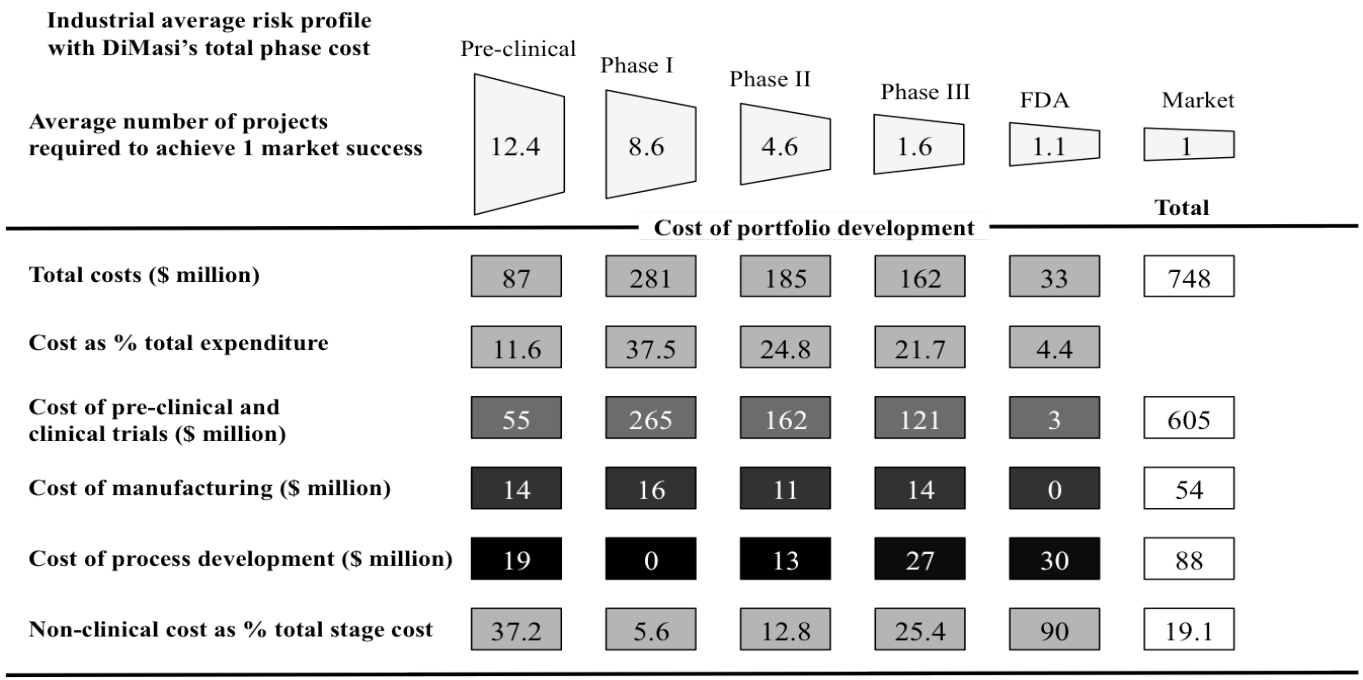


Figure 3.4 Cost evaluation of new biopharmaceutical product development.

The phase transition probabilities adopted in this evaluation are the industrial average scenario from Paul et al. (2010), with the total phase costs from DiMasi & Grabowski (2007). From these phase transition probabilities the average numbers of projects required to achieve 1 market success at each stage are calculated. The cost of pre-clinical and clinical trials are based on the number of projects at the current stage whereas the costs of manufacturing and process development for Phase I and II are based on the number of projects at previous stage because it is not known to the drug developer the outcome of the clinical trial.

The distribution of process development and manufacturing cost across development stages differs as the risk scenario changes. Defining early stage as from pre-clinical to Phase II and late stage as from Phase III to BLA submission, all early stage process development and manufacturing are running at risk. Therefore costs of process development and manufacturing from early stage increases faster than late stage as the development risk increases.

Table 3.7 Process development and manufacturing cost expected to ensure 1 market success in industrial scenarios featuring low, average, and high risk of failure.

Risk profiles	Optimistic (~29.8%)	Average (~11.7)	Pessimistic (~3.5%)
Early	28	72	239
Late	65	71	167

Note: Costs of process development and manufacturing are aggregated by their associated development stages. Development stages from pre-clinical to Phase II are defined as early stage and Phase III to FDA review are defined as late stage. All cost figures are in $ millions.

The impact of lower success rates and the resulting higher numbers of candidates at each phase on capacity requirement must also be considered in order to ensure sufficient process development labs are available as well as pilot and large scale GMP manufacturing facilities.

A complete collection of cost evaluations of new drug development under 3 risk assumptions with DiMasi and Paul's publications as major sources for phase costs is presented in Figure 3.5 and Figure 3.6.

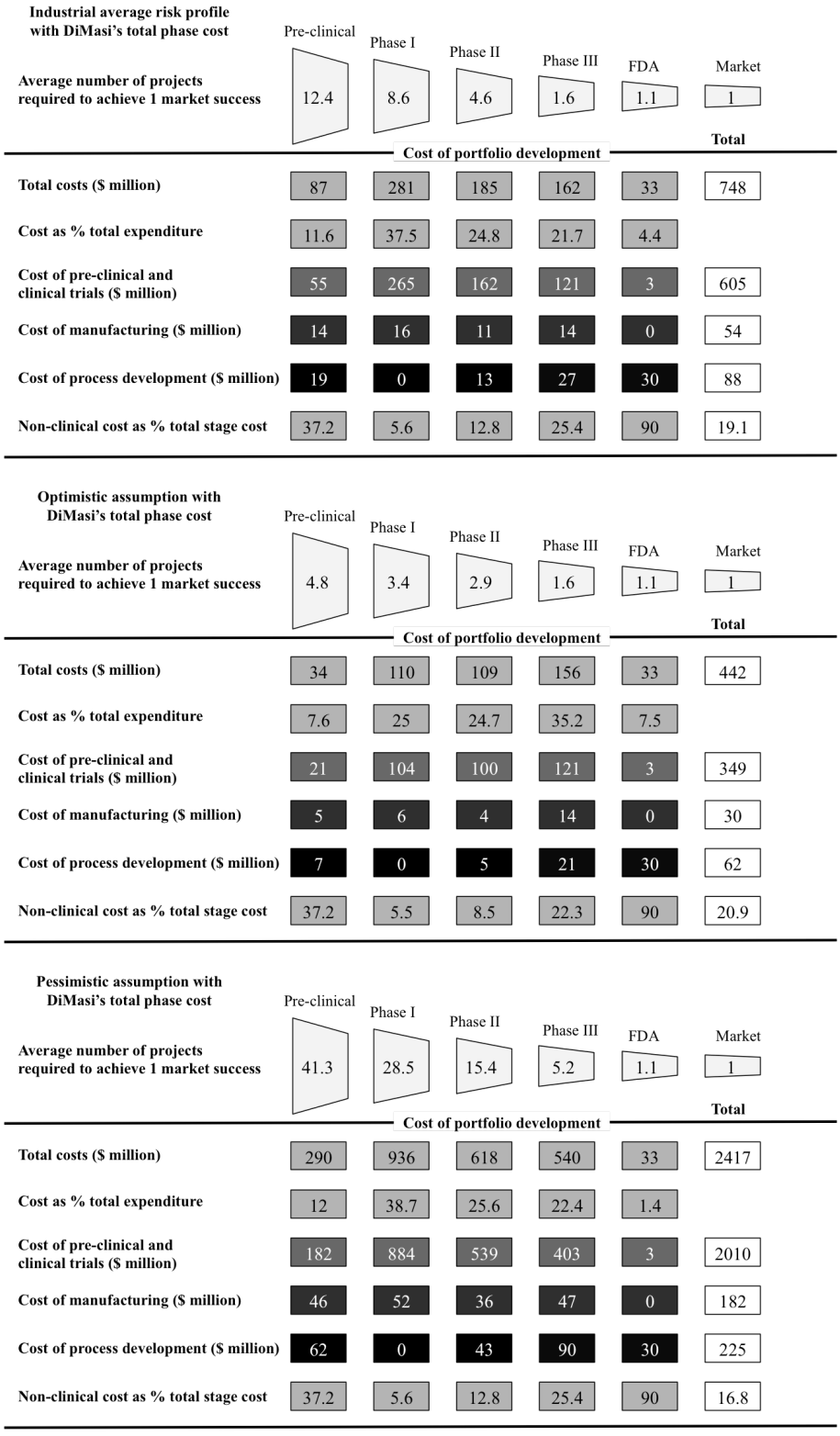


Figure 3.5 Cost evaluation of new drug development under 3 risk assumptions based on DiMasi's phase cost.

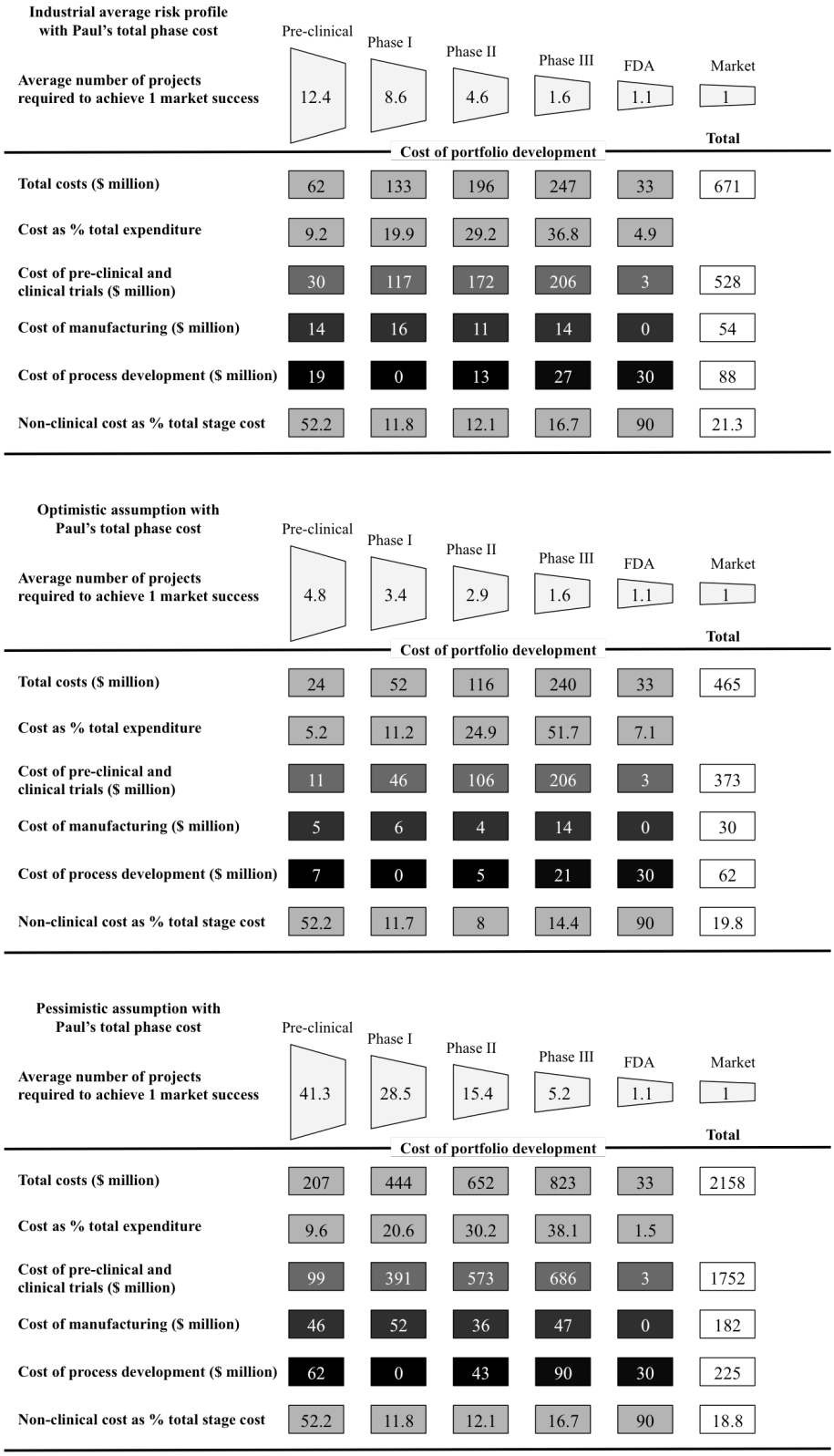


Figure 3.6 Cost evaluation of new drug development under 3 risk assumptions based on Paul's phase cost.

The total costs for each phase are summarized and their proportion to the total out-of-pocket cost calculated. In Figure 3.7, the division of new product development R&D spending is presented for 3 risk profiles, showing that Phase I is the major cost driver in biopharmaceutical new product portfolio development (37%) while the spending on FDA review stage is only 4.4% of the total cost. By evaluating the phase-wise cost composition for projects of low and high risk profiles, the model outputs show that there is a bigger market for early stage development projects in high-risk scenarios than in low risk scenarios.

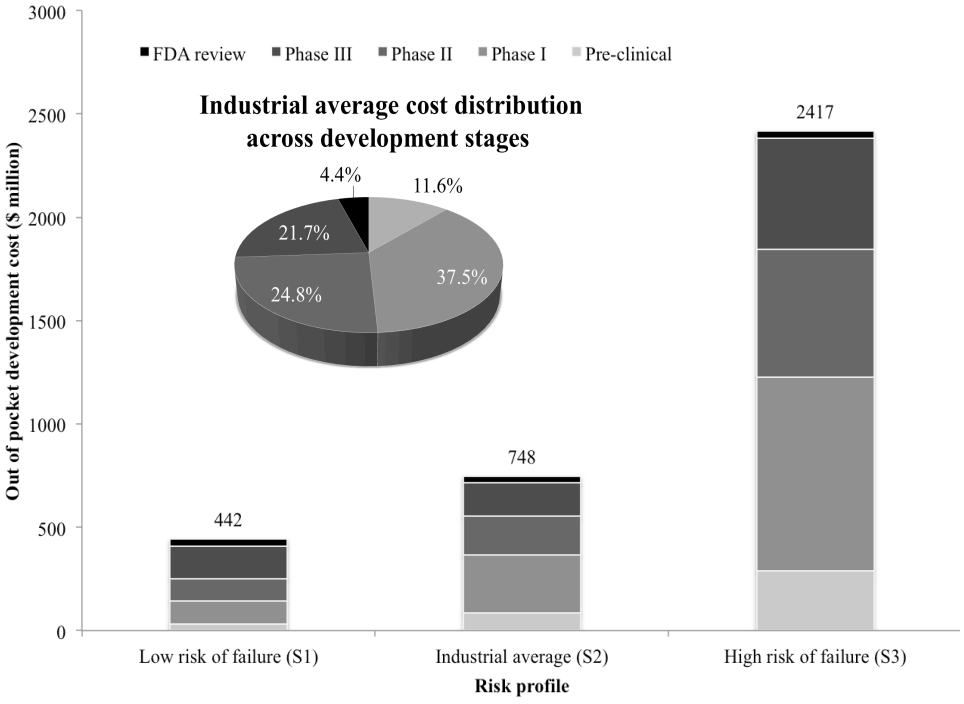


Figure 3.7 Cost distributions across development stages.

The cost distributions across stages are presented under 3 scenarios featuring average, low, and high risk of development failure. The pie chart within this figure emphasizes the industrial average cost distribution for pursuing 1 market successful product. These costs are out-of-pocket costs including the cost spent on failed projects.

For manufacturing and process development costs, the model summarizes their significance by development stages for 3 scenarios. Figure 3.8 shows the process development and manufacturing cost distribution across pipeline

development stages. Overall, the variation of success rate from 3.5% to ~12% or to 30% makes a 2.8 or 4.4 times reduction in manufacturing and process development costs. In the industrial average scenario, for each market success, the biopharmaceutical drug developer needs to allocate $72M of budget to process development and manufacturing activities from pre-clinical to Phase II stage, and $71M from Phase III to the BLA submission stage. For the low risk (success rate 29.5%) and high risk (success rate 3.5%) scenarios, these values are $28~239M for early phases and $65~167M for late phases. From low risk to high risk, the investment into manufacturing increases faster than process development. This is due to the assumption that there are more at risk investments into manufacturing than process development, therefore increasing the number of projects required causes more increase in manufacturing cost. For the industrial average, the cost of manufacturing should be approximately 62% of the cost of process development. At the low risk scenario, the drug developer should be focusing on the late stage manufacturing and process development, as they are the majority of investment. At the high risk scenario, the cost ratio of 1) early stage process development, 2) late stage process development, 3) early stage manufacturing, and 4) late stage manufacturing is approximately 1:1.15:0.95:0.6. For company with large development portfolio, cost reduction methods such as streamlined technology platform for process development and manufacturing at early stage are useful.

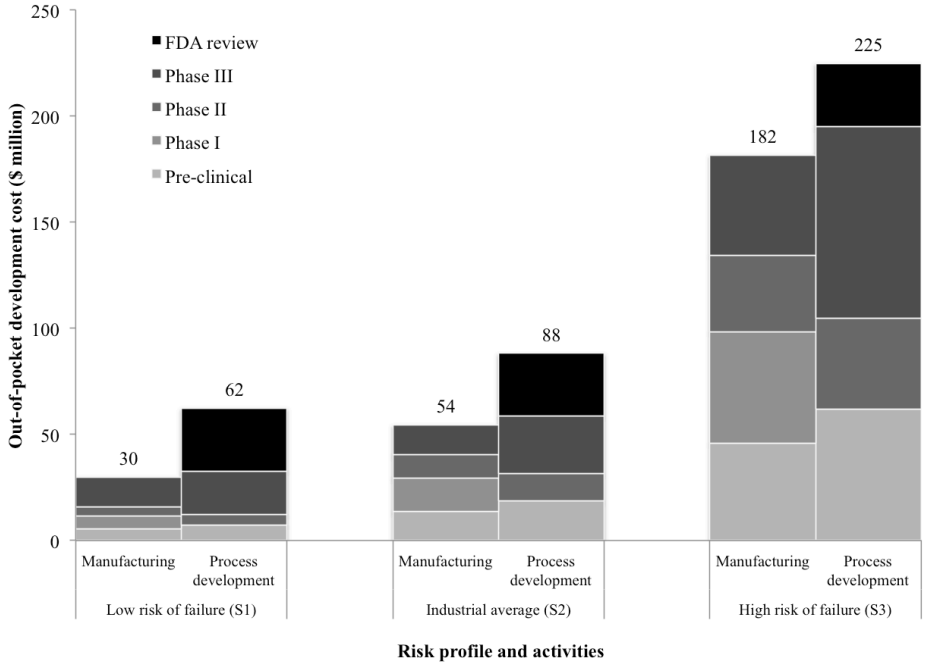


Figure 3.8 Process development and manufacturing cost distribution across development stages.

The process development and manufacturing cost distributions across stages are presented under 3 scenarios featuring average, low, and high risk of development failure. These costs are out-of-pocket costs including the cost spent on failed products.

3.6.2 At-risk sensitivity analysis

One of the key decisions in biopharmaceutical new product development process is the planning of Phase III process development so that it meets the supply requirement of the clinical trials. Considering the high cost of Phase III process development, the decision maker faces the trade-off between higher cost and potential delay. The zero delay decision would place a significant portion of process development activity before Phase III clinical trial starts, which could lead to maximum investment lost if the project failed at Phase II.

This analysis used the standard durations from base case as the mean value of activities. The uncertainties were introduced by applying normal distributions to the durations of activities. For Phase III stage, the activities

and time points of concern are the Phase III process development activity, Phase III clinical trial preparation period, and the time point of Phase II end and Phase III starting. A 4 months standard deviation was applied to the 24 months duration of Phase III process development activity, indicating that there was nearly a 95% chance that the duration was within 16-32 months range (2 times the standard deviation from the mean value). By defining the cost invested to the process development activities on the failed projects as "risk cost", this cost-risk trade-off is presented in Figure 3.9 for a development portfolio of average development risk.

The likelihood of causing delay in critical path can be reduced by prolonging the duration of process development running at risk, i.e. starting the process development activity early. However, the effect diminishes as the risk reduces, and it is almost impossible to remove any chance of delay. Therefore in this analysis, a 10% likelihood of delay is introduced as the maximum tolerance of risk from the decision maker. To achieve this level of safety, the process development activity should start at 14.2 months ahead of the Phase III decision, which implies that potentially $18 million investment is made at risk and could be lost if the projects failed to proceed to Phase III. The risk cost is affected by the portfolio risk profile. A high-risk profile increases the risk cost of reducing clinical trial delays.

The above analysis is based on the assumption that the clinical trial preparation time is certain, which is not in some cases. Applying a 3 months standard deviation to the length of Phase III clinical trial preparation time will increase the difficulty of reducing the risk of delay. To achieve the same level of risk tolerance, the risk duration should be increased to 15.5 months which translates into a risk cost of $19.7 million. On the other hand, if the level of uncertainty reduces and the standard deviation of process development length is 3 month, 12.9 months of risk duration and $16.4 million risk cost would be adequate in achieving the target tolerance.

If the company developed a technology that reduces the expected length of process development, it will reduce the risk cost significantly. For example,

with the industrial average risk profile, if this technology is capable of reducing the expected length of process development by 6 months and the standard deviation by 1 months, a 25% reduction, the resulting risk cost required to achieve the same level of safety would be $8.9 million, and risk duration 7 months. The value of this technology is therefore the reduction of risk cost for approximately $9 million.

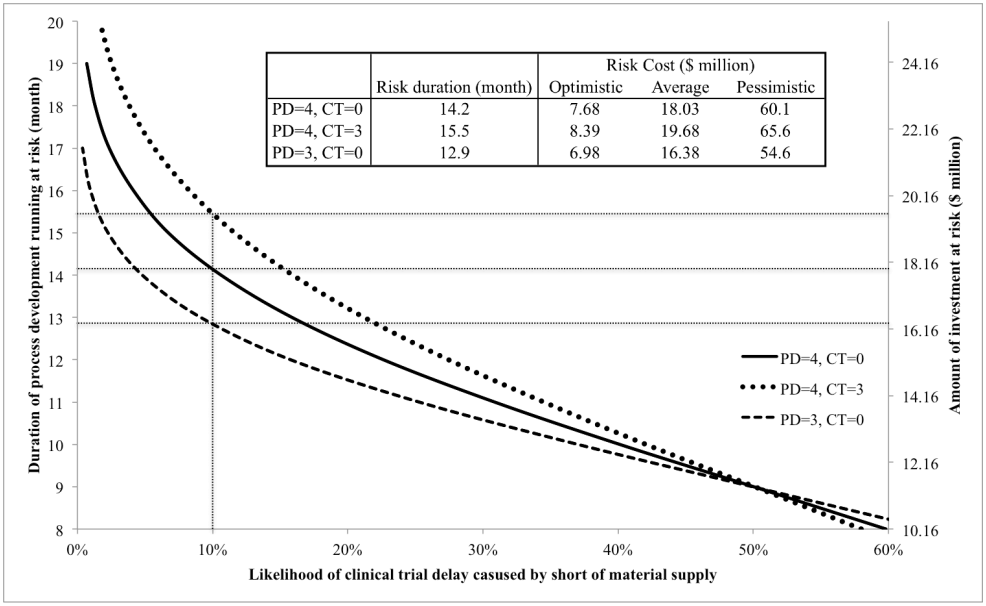


Figure 3.9 Trade-off between at risk investment into Phase III process development and having delay to the product development process.

The Phase III process development activities are partially running at risk in order to avoid causing delays in supplying material to Phase III clinical trials. Due to the uncertainty within the duration of the activity itself that is quantified as a Gaussian distribution here, there is the possibility of causing delay to the critical path of development. Starting the process development at risk earlier than the expected required timing could mitigate the likelihood of delay, however this will increase the investment at risk that is defined as the cost to the projects that are going to fail. This analysis applied 3 levels of uncertainties to the 3 scenarios of risk profile. The low level of uncertainty assumes all information to be certain, apart from the length of the process development subjected to a 3 months standard deviation to the expected 24 months length (PD=3, CT=0). The medium level of uncertainty increases the standard deviation of process development length to 4 months (PD=4, CT=0). The high level of uncertainty maintains the variance of process development length while assuming the period between Phase III decision and the actual demand to be uncertain and subjected to a 3 months standard deviation to the expected 18 months length (PD=4, CT=3). A maximum tolerance of 10% likelihood of delay is applied to various levels of uncertainties and risk profiles yielding the timing and cost required to achieve the level of safety.

3.7 CONCLUSION

This chapter benchmarks the cost to develop and manufacture therapeutic biologics across the drug development lifecycle, emphasizing the cost distributions across both development stages and clinical and non-clinical activities. This was achieved with the biopharmaceutical drug development lifecycle model described in Chapter 2 that captured the costs, durations, risks and interdependencies of both the clinical and non-clinical activities. The non-clinical activities were broken down into process development and manufacturing. A detailed analysis is presented of the process development and manufacturing costs across the biopharmaceutical drug development cycle on a single drug and portfolio basis. The non-clinical budgets needed at each phase of development to ensure a market success each year were estimated for three representative clinical risk profiles and two industrially relevant average stage cost alternatives. The costs of process development and manufacturing activities at each stage and their proportions of the total cost were further investigated in a sensitivity analysis with changing risk and cost scenarios. The economic implication of efforts that minimize the risk of delay was explored through a probabilistic approach that applied uncertainties to the durations of activities. The analysis lays down the foundation for portfolio management optimization based on cost and risk related parameters, which is discussed in the next chapter.

CHAPTER 4

STOCHASTIC OPTIMIZATION OF BIOPHARMACEUTICAL PORTFOLIO DEVELOPMENT DECISION-MAKING UNDER RESOURCE CONSTRAINTS AND UNCERTAINTIES

4.1 INTRODUCTION

In Chapter 3, the cost evaluation of biopharmaceutical portfolio development was presented and the benchmark of cost distributions across development stages and activity categories were captured using a drug development lifecycle cost model. In this chapter, the stochastic optimization tool is implemented to assist biopharmaceutical portfolio management decision-making with a diversified product candidate pool.

The pharmaceutical industry has suffered from diminishing R&D productivity and increasing R&D cost over the past decade. Portfolio management decisions are critical to pipeline development especially when exposed to outside competition such as follow-on drugs. Studies have indicated that most of the follow-on drugs had already started clinical trials before the approval of the corresponding original (first-in-class) drugs (DiMasi & Faden 2010). Published studies on R&D portfolio management have focused on decisions related to candidate selection and capacity sourcing, but have not concentrated on the issues of budget and capacity planning in different stages of development that can impact the progression between development milestones. By implementing the stochastic optimization tool described in Chapter 2, the drug portfolio developer is able to obtain more information regarding the actual budget and capacity required in various development stages, and gains insight into the cash flow characteristics of the optimal solutions produced by the algorithm. Therefore better outcomes can be achieved from the execution of optimal portfolio management strategies.

The case study proposed in this chapter investigates scenarios where the product candidates in the portfolio are all novel in-house candidates starting

at the pre-clinical stage as well as scenarios where the product candidates available for selection in the starting portfolio include products at different stages of development, which can be the case for some drug development portfolios. Choosing a product candidate that is in a later development stage can be beneficial as it is more likely to reach the market and the remaining cost of development is less than that for a candidate that is at an earlier development stage. However, the drug portfolio developer may not have direct access to such products that are owned by other organizations. Acquiring these products normally involves a large amount of upfront cost, which can be associated to the cost spent to bring the product to the current stage. In this chapter, the impact of upfront cost and its interaction with budget constraints is presented and analysed under the scenario that product candidates are at different stages.

The remainder of this chapter is structured as follows. Section 4.2 introduces the tool implemented in this chapter. The case study input parameters to this tool are presented in Section 4.3 as well as the configurations for resources constraints and algorithm running parameters. In Section 4.4, the optimization of biopharmaceutical portfolio management is presented under budget and capacity constraints, and the impact on the cash flow for clinical and non-clinical activities is presented. Finally, Section 4.5 extends the analysis to a more diversified candidate pool with options to acquire outside products that are more advanced in the drug development process.

4.2 TOOL DESCRIPTION

The stochastic optimization tool implemented in this chapter was originally proposed in Chapter 2. The tool is comprised of 1) an evaluation engine capable of performing Monte Carlo simulation and dynamic simulation for integration of resource constraints with drug development uncertainties; 2) an multi-objective evolutionary algorithm for optimizing drug development portfolio management decisions based on the results produced by the

evaluation engine; and 3) a data management system to collect information for further analysis during the running of the tool.

For the purpose of the analysis presented in this chapter, the tool was operated with its full functionality, with all the features of the 3 key components turned on. However, crucial inputs regarding the development characteristics of product candidates, the configuration of resource constraints, and the set up of running parameters were still required for formulating the case study. These are described in the following section.

4.3 CASE STUDY SET UP

4.3.1 New product development process

In this study, we used the previously established new product development process in biopharmaceutical industry. This process was also adopted in the analysis of benchmarking the cost of developing biopharmaceutical product portfolio aiming at one market success in Chapter 3. The model captured the process from the pre-clinical phase through to the product market launch. Manufacturing and process development activities supporting the pre-clinical and clinical trials were planned at risk so that no delays were caused in the critical path of clinical development. The dependencies of these activities were shown in Figure 3.1. Every square represents an activity that consumes budget and time of the drug developer in this model. Activities on the critical path were subjected to development failure, which was addressed by transition probabilities in Monte Carlo simulations.

The benchmark results for developing a single biopharmaceutical product presented in Chapter 3 were used as inputs in this case study, and are summarized in Table 4.1.

Table 4.1 Durations and costs for developing a single biopharmaceutical product.

		PC	I	II	III	FDA
CT	Cost ($million)	4.4	31	35	77	3
	Duration (year)	1	1.6	2.4	2.7	1.5
PD	Cost ($million)	1.5	0	1.5	10	27
	Duration (year)	1	0	0.5	2	1.5
Manu	Cost ($million)	1.11	1.27	1.27	9	0
	Duration (week)	6	5	5	13	0

Note: CT – clinical trial. PD – process development. Manu – manufacturing. PC – pre-clinical stage. I to III – Phase I to Phase III stage. FDA – FDA review stage.

4.3.2 The candidate pool

In order to illustrate the functionality of this tool, the candidates in this case study were designed such that no obvious solutions can be derived by using simple rules such as maximum expected NPV. Risk-reward trade-offs were specifically built in by varying the transition probabilities of products and their potential market values.

The candidates were identical in terms of durations and costs of the activities, but differed in their chances of successfully reaching the market. Table 4.2 presents the risk profiles for candidates from low, medium, and high risk groups, which were the same as the phase transition probabilities used in Chapter 3 for benchmarking the development cost of developing drug portfolio aiming at a single market success.

Table 4.2 Candidate risk profiles.

	PC	Phase I	Phase II	Phase III	FDA review
Low risk	70%	85%	55%	70%	91%
Medium risk	69%	54%	34%	70%	91%
High risk	69%	54%	34%	21%	91%

(Continued) Note: The transition probabilities from medium risk group are from published sources on industrial average pharmaceutical development cost study (Paul et al. 2010); The low risk transition probabilities are derived from the higher values of published transition probabilities for each phase (DiMasi & Grabowski 2007; Nelson et al. 2010; Bogdan & Villiger 2010); The high risk groups take on the transition probabilities of the medium group from pre-clinical to Phase II, but the Phase III probability is lower to reflect the case for indications such as Alzheimer's disease.

The candidates were also designed to have the same, positive expected NPV, regardless of their risk profiles. In order to achieve this, their market values were tuned accordingly. The market value of a product candidate was defined as the sum of all discounted future cash flows brought by the product. It was evaluated after all the costs related to marketing and manufacturing of the products have been accounted for, therefore in the model simulation the market value was realized once the candidate reaches the market. For the low, medium, and high-risk candidates, their respective market value was set to \$1500 million, \$5200 million, and \$21000 million respectively. In practice, the market value of a candidate can be easily translated into peak sales of the product once the sales curve and product life is determined. For instance, assuming the product peak sales occurs at the 11^{th} year of entering the market, and the product life is 21 years, \$1500 million market value can be viewed as \$600 million peak sales using the sales curve introduced by Bogdan & Villiger (2010) at a gross margin of 50%.

Thirty product candidates were created from these three risk groups, with each risk profile represented by 10 product candidates. The number of selections of product candidates in each risk group reflected the preference of solutions in the risk-reward trade-offs.

4.3.3 Budget constraints

The budget constraints in this case study were addressed by setting up an annually updated maximum value for development spending. The value of the budget constraint can directly impact the selection of product candidates.

However, budget constraints that are above a certain value can operate in a similar fashion to unlimited cash flow. Hence it was important to determine an effective range of budget constraints for developing this particular candidate pool. This was derived based on the maximum requirement of funds in more than half (>50%) of situations.

The budget limits in this case study were established based on the lower bound of the maximum budget requirement to ensure the influence of budget constraint on the selection of candidates. Under this lower bound of maximum requirement of budget, the budget constraint has impact on most of the portfolio management decisions. Table 4.3 describes the procedure to determine the lower bound of maximum annual budget using binomial distributions. With the 10 products from each risk group at the pre-clinical stage, the number of products reaching each development stage can be derived by applying the binominal model with the phase transition probabilities of each stage. The minimum numbers of products reaching each stage in more than 50% of scenarios were used for determining the annual cost for developing products from each risk group. Finally, combining the annual costs from the three distinct risk groups yielded the defined lower bound of annual budget requirement, which was $257 million during the Phase I stage. Because the binomial probabilities presented in Table 4.3 included a scenario in which the actual number of projects was higher than the target number, the upper bound of the maximum budget requirement can be well above $257 million. In this case study, the budget limits were therefore set to be from $50 million to $300 million with increments of $50 million.

Table 4.3 Estimation of the lower bound of the maximum annual budget requirement for development of 30 biopharmaceutical R&D projects.

Development stages	PC	I	II	III	FDA
Duration (Year)	1	1.6	2.4	2.7	1.3
Cost of clinical trials ($million)	4.4	31	35	77	0.3
Phase transition probability					
Low risk projects	0.7	0.85	0.55	0.7	0.91
Medium risk projects	0.69	0.54	0.34	0.7	0.91
High risk projects	0.69	0.54	0.34	0.21	0.91
Probability of reaching this stage					
Low risk projects	1	0.70	0.60	0.33	0.23
Medium risk projects	1	0.69	0.37	0.13	0.09
High risk projects	1	0.69	0.37	0.13	0.03
Number of projects reaching this Phase with >50% probability from 10 projects					
Low risk projects	10	7	6	3	2
Medium risk projects	10	7	4	1	1
High risk projects	10	7	4	1	1[a]
Binomial probability of having the above number of projects or more at these stages					
Low risk projects	1	0.65	0.62	0.69	0.71
Medium risk projects	1	0.62	0.55	0.74	0.60
High risk projects	1	0.62	0.55	0.74	0.24[a]
Cost per year ($million/year)					
Low risk projects	44	135.63	87.50	85.56	0.46
Medium risk projects	44	135.63	58.33	28.52	0.23
High risk projects	44	135.63	58.33	28.52	0.23
Budget required per year ($million/year)	132	257	118	101	0.52

Note: The repeated trials are constructed based on 10 independent project candidates created for each group with distinct risk profiles. For each development stage, the probability of reaching that stage is calculated using phase transition probabilities of the previous stages. The number of project candidates reaching a certain stage given 10 independent trials is therefore a binomial distribution from

(Continued) which the lower bound of the annual budget requirement can be defined as the fund capable of supporting the number of projects in more than 50% of all the possible scenarios.
[a] The probability of getting one or more projects to FDA review stage in high-risk group is lower than 50% from 10 candidates. This exception is made so that there is cost related to high-risk projects at this stage.

In the model simulation, any lack of funds caused the activities to halt until budget was updated in the following year. Therefore a delay caused by a budget constraint could last potentially as long as one year. Delays in development affect the final market launch of the product, and in turn affect the product's profitability. Previous studies indicate that delays to market launch may result in loss of a competitive position (e.g. Kennedy 1997). Hence, for every year of delay, the model assumes that the product market value was reduced by 35%.

In practice, the real budget limits can be obtained through the study of company R&D expenses after deducting the non-cash items such as depreciation.

4.3.4 Capacity constraint

The capacity constraint in this case study was set up to determine the optimal capacity level, and to maximise the utility under the constraint through portfolio selection. Because of the probabilistic nature of biopharmaceutical new product development, capacity budgeting cannot be accurate all the time. The mismatch—too much capacity with too few products, or vice versa—will cause inefficiency and therefore damage the value of the portfolio.

The upper bound of effective levels of capacity constraint was determined by configuring the capacity level such that in almost all (99%) cases the capacity requirement for commercial manufacturing could be fulfilled in-house. In Figure 4.1, the capacity of commercial manufacturing was translated into the amount of portfolio market potential that can be achieved through in-house production. It was assumed that with every 120kg/year

increase in production, $2000 million in market value could be realized, based on the selling price of monoclonal antibody products. The case study focused on capacity constraints from 120kg/year (~50% probability of realizing the full portfolio market value) to 840kg/year (>99% probability of realizing the full portfolio market value) with 120kg/year increments in capacity to explore their impact on the risk-reward performances and the corresponding optimal portfolio selection decisions (see Figure 4.1).

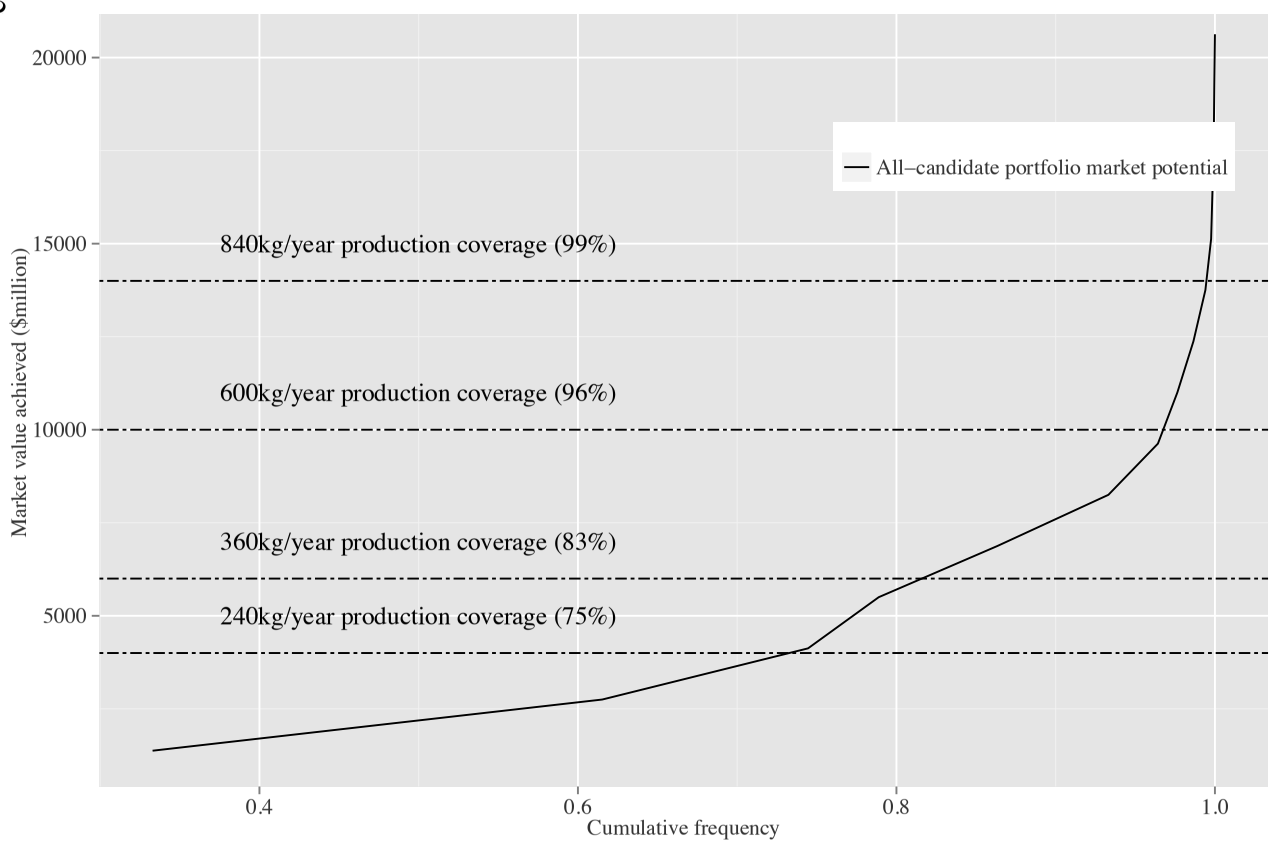


Figure 4.1 Cumulative frequency distribution of the all-candidate portfolio market potential from Monte Carlo simulation trials given the risk of product clinical trial failure.

Effective levels of capacity constraints are indicated by the dotted lines. The resulting capacity requirements were calculated in terms of total portfolio market value, assuming for every extra $2000 million in market potential, an extra 120kg/year production was needed. Market value was defined as the sum of all discounted future cash flows brought by the product.

4.3.5 Optimal configuration for population size and generations

As discussed in Chapter 2, before implementing the non-dominated sorting genetic algorithm NSGA-II, trial runs have to be performed to find the optimal configurations for running the algorithm. A hypervolume-based approach was implemented to compare the performance of the algorithm under various running parameters, in which hypervolume represents the proximity to the real Pareto front. In this approach, the total number of evaluation was fixed at 5000 with the population size varying from 20 to 100. Consequently the maximum numbers of generations were from 50 (population size 100) to 250 (population size 20). The hypervolume of the Pareto front of the final generation was calculated to represent the overall performance of the algorithm in the multi-objective space. The optimal population size was 80 as it yielded the highest hypervolume value compared to other configurations of population size.

With an optimal population size of 80, the algorithm was implemented without any resource constraints for 30 repeated trials. As illustrated in Figure 4.2, the hypervolume starts to converge after around 20 generations, and fully converged before 50 generations. Different independent trials yield very little variations in terms of hypervolume, and they tend to converge with the increases of the generations. Therefore for the problem specified in this case study, it was sufficient to have 30 independent trials running for 50 generations to produce a quality Pareto optimal front consistently.

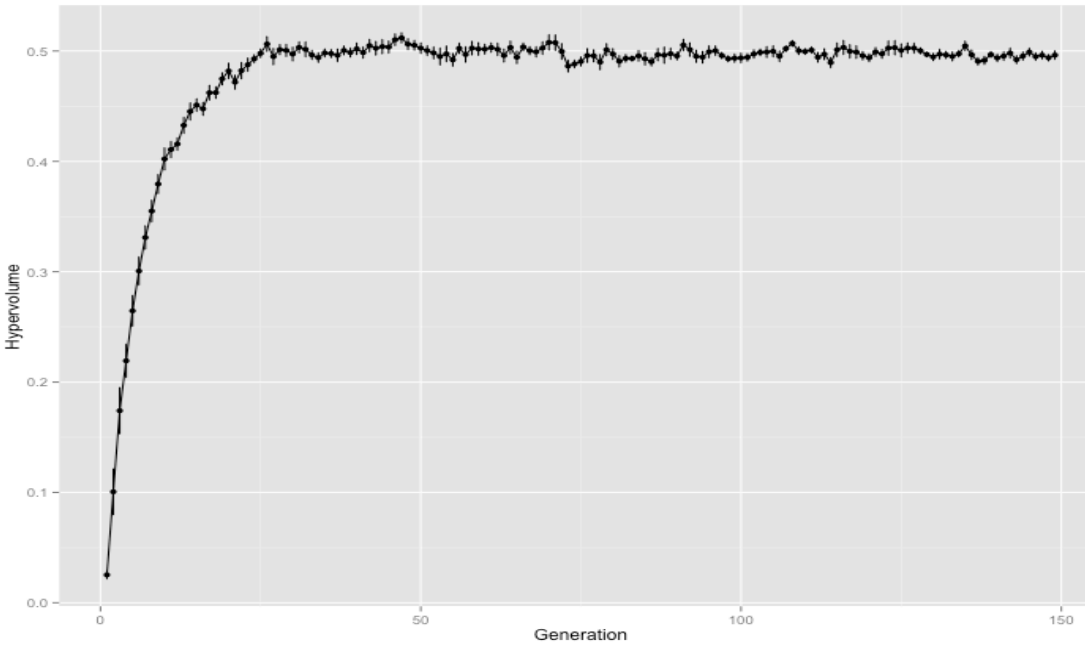


Figure 4.2 The convergence of hypervolume of Pareto front for 30 independent trials of genetic algorithm.

The error bars are the standard errors from the distribution of hypervolume across 30 trials.

4.4 RESULTS: OPTIMIZATION UNDER RESOURCE CONSTRAINTS

In this section, the stochastic optimization tool was implemented under various configurations in order to showcase its functionality under possible industrial scenarios. The boundaries of optimal performances were explored in the presence of constraints on both the budget and manufacturing capacity fronts. Optimal solutions generated from evolutionary algorithms are discussed and detailed analyses of their distinct economical and operational characteristics presented.

4.4.1 Budget constraints

Figure 4.3 shows the impact of budget constraints on decisions in portfolio composition and the resulting objective values. The resulting Pareto fronts demonstrate the trade-off between the conflicting objectives of reward, in

the form of the average positive NPV, and risk, in the form of p(NPV>0), as illustrated by the negative relationship between them. As the budget constraints are relaxed, improvements can be observed in both optimization objectives as the Pareto front shifts to the right. Hence for a given p(NPV>0) value, the higher the budget limit the higher the average positive NPV . However, the effect of improvement diminishes quickly as the budget limit gets closer to the lower bound of the maximum annual budget requirement.

Solutions under the more relaxed budget constraints perform better than solutions under the more tight budget constraints in the high p(NPV>0) value region. Since the average positive NPV value only takes into account the NPVs that are positive, the higher the p(NPV>0) value, the more reliable the average positive NPV value. Hence the profitability of a solution can be compared to another only when they have a similar p(NPV>0) value. In the region where p(NPV>0) is greater than 0.5, solutions at the $300 million budget constraint dominate the solutions of all other Pareto fronts.

From a decision-maker's point of view, the same level of safety can be achieved from different budget setups by constructing the portfolio that matches the budget. As described in Figure 4.3, to achieve a p(NPV>0) value of 0.69 the company should focus on low risk projects when the budget is at $150 million. When the budget rises, it is more profitable with the same level of safety to shift the focus to more medium and high-risk projects.

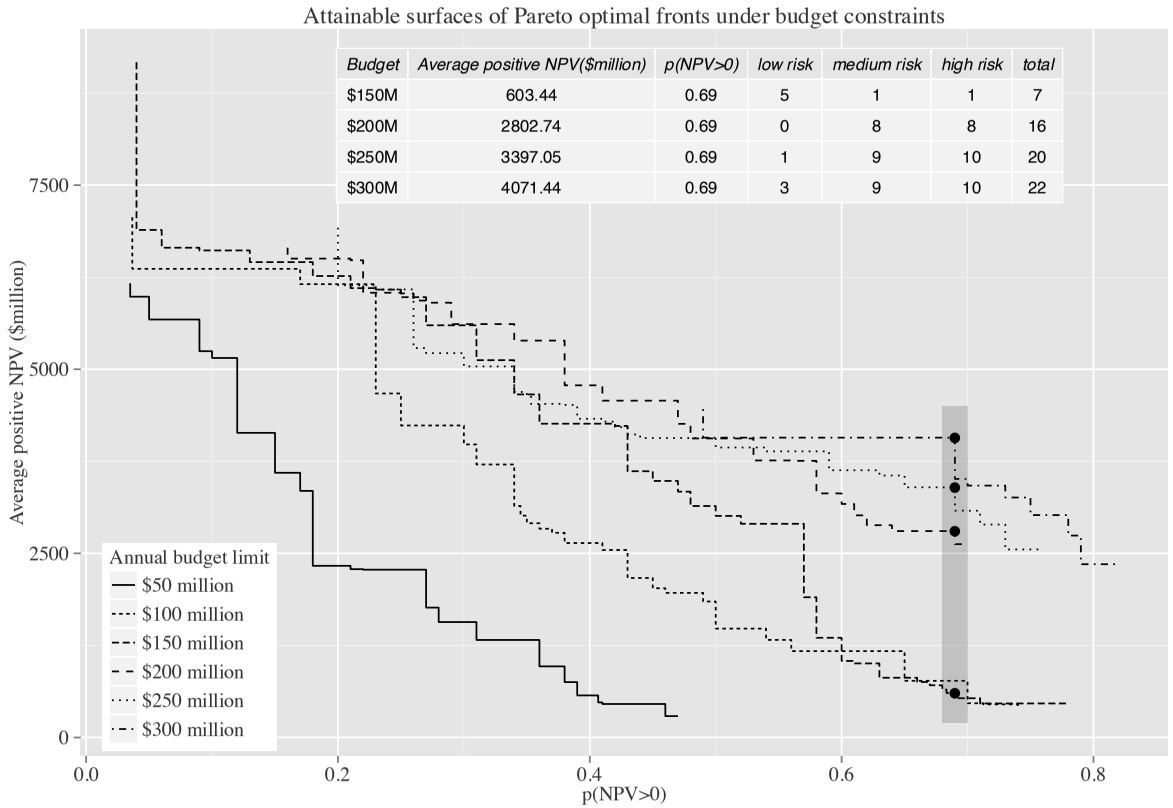


Figure 4.3 Attainable surfaces of Pareto optimal fronts under various annual budget limits.

Evolutionary algorithms are implemented to efficiently search the decision space for optimal solutions. 2 objectives: the probability of resulting a positive NPV, i.e. p(NPV>0) and the average positive NPVs generated by multiple Monte Carlo trials from 1 single solution are the driving force for evolution through generations. For each budget limit scenario, 30 independent trials of indicator-based evolutionary algorithm (IBEA) are performed to process a randomly generated initial generation of 80 candidate solutions through 50 generations. The Pareto optimal fronts from the 30 independent trials of each scenario are extracted by a non-dominated sorting algorithm and plotted in this graph with x-axis representing p(NPV>0) value and y-axis representing the average positive NPV. Specifically, solutions with similar p(NPV>0) values from different Pareto optimal fronts are observed and their decisions presented in the table.

Further investigation into the cash flow distributions from optimal solutions unveiled more details of portfolio development. Figure 4.4 illustrates that for solutions with a 0.79 p(NPV>0) value, the maximum average annual out-of-pocket cost is just right under the budget level for the scenarios at the \$150M, \$200M, \$250M, and \$300M annual budget levels,. The years with the most spending on the development timeline are the 3rd, 4th, and the 6th year, with the 6th year being the year of maximum annual spending for a solution that relies most heavily on low risk projects (5L, 1M, 1H), and the 3rd year for solutions that lean towards medium and high risk projects.

Costs originated from process development, manufacturing, and pre-clinical & clinical trials are colour-coded in Figure 4.4. Pre-clinical & clinical trials are the most cost-consuming in portfolio development. The costs of process development are mainly incurred in the 1st & 2nd year, the 4th to the 6th year, and the 9th & 10th year, which are often followed by a short period of manufacturing.

The out-of-pocket costs of non-clinical activities are summarized in Figure 4.4, in which comparisons of costs distributed to process development and manufacturing activities are made among the optimal solutions with the same p(NPV>0) value. Phase III process development cost tops the non-clinical costs of in portfolio development under budget constraints, followed by the manufacturing cost for late stage development supply. The number of products at different development stages is the key driver of non-clinical costs. At FDA review stage, the cost of process development for the optimal solution under \$150 million budget is higher than the one under \$200 million budget, since the former has a slightly higher average number of products reaching the stage.

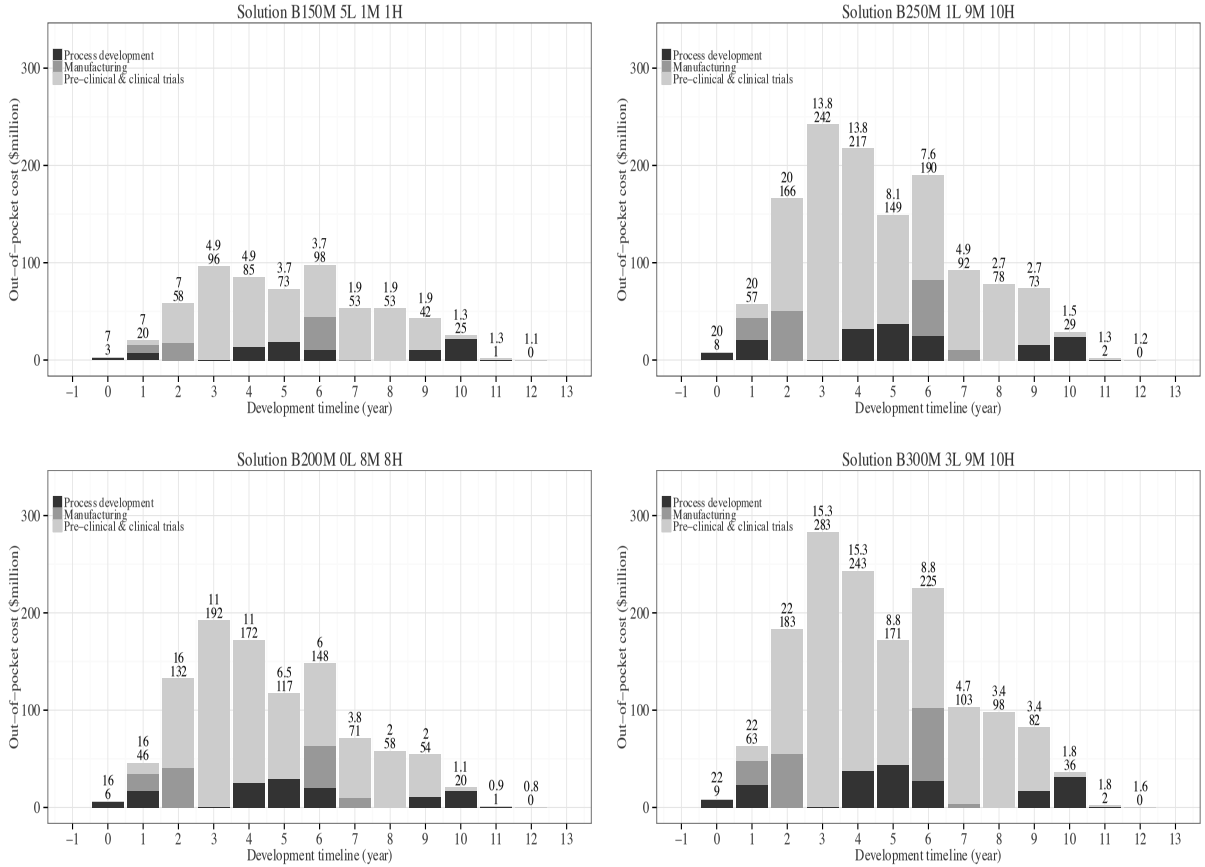


Figure 4.4 Cost distributions on development timeline for optimal solutions, highlighted by origin of activities.

Optimal solutions from budgetary constraints of $150, $200, $250, and $300 million that yield 0.69 in p(NPV>0) value were picked and their cost distribution across the development timeline were presented. Cash flow data were collected from each Monte Carlo simulation and averaged to calculate the expected figures. Out-of-pocket costs originated from process development, manufacturing, and pre-clinical & clinical trials were highlighted in different degree of grey. The expected numbers of projects on the timeline were displayed on top of the total expected out-of-pocket costs at the bar tops. Titles from each sub-figure indicate the annual budget level and the selection toward low, medium, and high risk as well as market potential projects. E.g. B150M 5L 1M 3H means is an optimal solution from $150 million budgetary constraint scenario with 5 low risk, low market potential, 1 medium risk, medium market potential, and 3 high risk, high market potential projects.

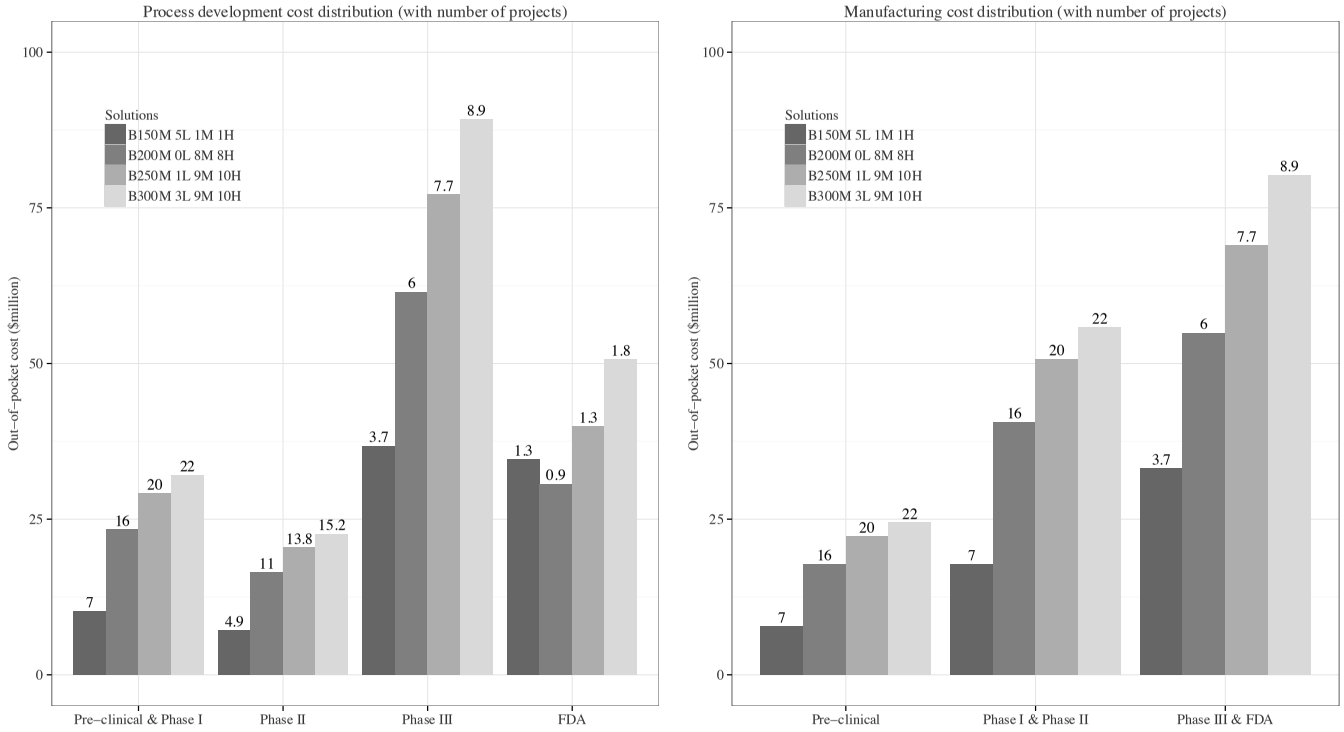


Figure 4.5 Stage costs of optimal solutions for process development and manufacturing activities.

Optimal solutions from budgetary constraints of $150, $200, $250, and $300 million that yield 0.69 in p(NPV>0) value were picked and their process development and manufacturing cost distribution across the development stages were presented. The numbers on top of the bars are the average numbers of products at the stage that is accounted for in calculating the non-clinical costs.

To better understand the mechanism and effect of the annual budget constraint, the optimal solution from the $300 million constraint with a 0.79 p(NPV>0) value was singled out as a performance checker. Simulation results of the cash flow performance of this solution under other budget constraints are presented in Figure 4.6, with the costs from different development stages colour-coded. Varying from $100 to $300 million, the annual budget constraints have a significant impact on the average portfolio marketing time. With an annual budget constraint of $100 million, it is unlikely that the portfolio products would reach the market within the modelling time horizon of 14 years. When the limit changes from $200 million to $300 million, the average time to market shortens from 13 years to 12 years, with the average finishing time of Phase I decreasing from the 5th year to the 4th year and Phase II from 9th year to 7th year. The time saved by increasing the annual budgetary limit from $300 million to $400 million is negligible, as in both cases the portfolio products reach the market at the same year, although in the $400 million scenario the Phase II activities finished slightly earlier than in $300 million scenario. Therefore in this case the ideal budget level is $300 million, as increasing the budget beyond this value has little impact on the portfolio profitability. Lowering the budget level does provide smoother spending curve, but at the expense of delaying the time to market and hence the timing for revenue.

Budget planning that is more flexible than a fixed annual cap can be derived from this analysis. From year 0 to 3, there is a sharp increase in the requirement of funds that should be accounted for to safeguard the development process. Pre-clinical and Phase I costs are the main cost drivers during this time period. From the 4th year to the 6th year, while the total requirement of funds stays at a similar level, its distribution shifts to Phase II and III development stages. From the 7th year, a lower level of funds is required to focus on Phase III clinical trials and the process development activities in preparation of commercial production, till the years 11 and 12 when the product finally enters the market.

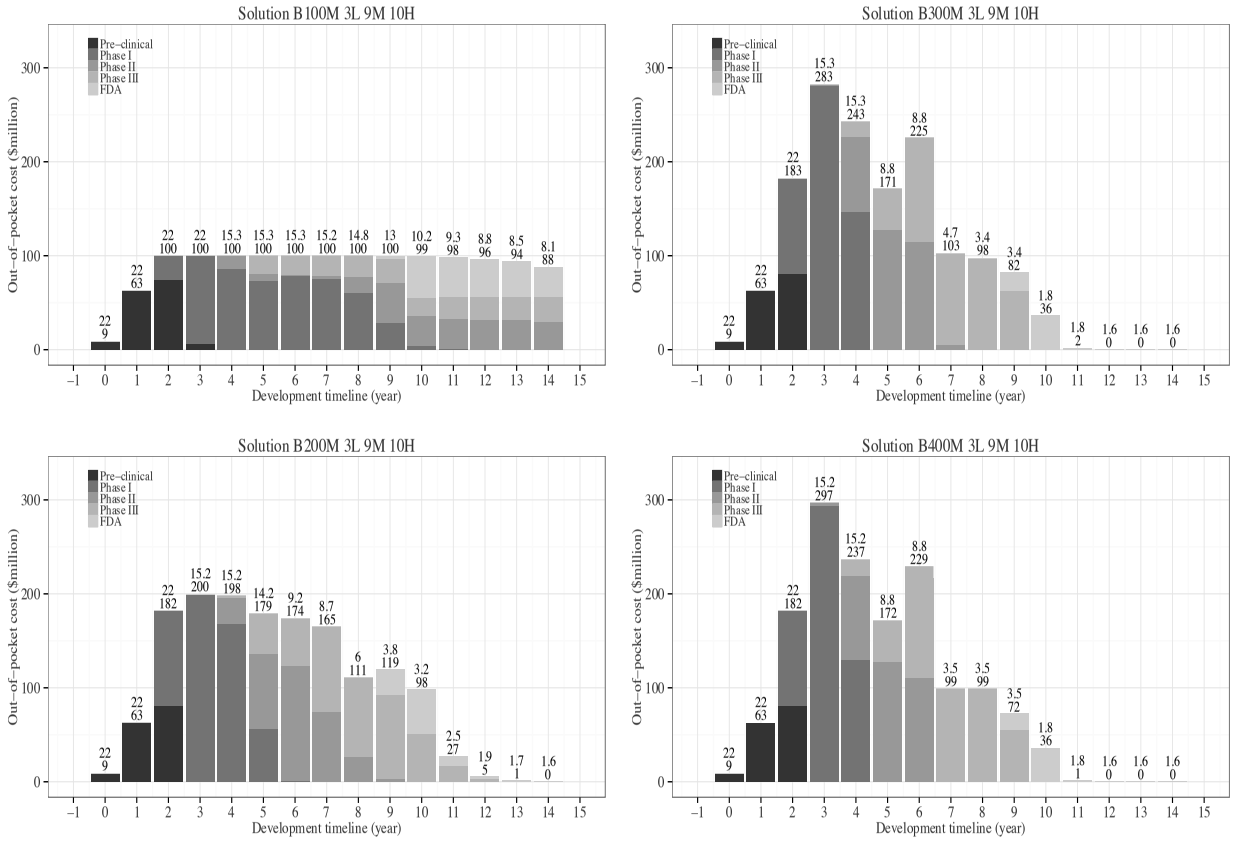


Figure 4.6 Cost distributions on development timeline for optimal solution from budgetary constraint of $300 million, highlighted by development stages.

Optimal solution from budgetary constraints of $300 million that yield 0.69 in p(NPV>0) value was picked and its cost distribution was simulated under other budgetary constraints ranging from $100 to $400 million. Cash flow data were collected from each Monte Carlo simulation and averaged to calculate the expected figures. Out-of-pocket costs originated from various development stages were highlighted in different degree of grey. The expected numbers of projects on the timeline were displayed on top of the total expected out-of-pocket costs at the bar tops. Titles from each sub-figure indicate the annual budget level and the selection toward low, medium, and high risk as well as market potential projects. In this figure the selection of projects remains the same for all budgetary constraints.

4.4.2 Capacity constraint

This analysis explored the impact of clinical and commercial capacity constraints on solution performances and portfolio selection decision-making. Drug developers are often faced with the decisions of future manufacturing capacity while there exists the possibility of product failure in clinical trials. The setup can also solve the optimal capacity configuration at a given level of safety.

For pre-clinical, Phase I, and Phase II stages, decisions concerning the manufacturing capacity has little impact on the capacity of manufacturing for commercial purpose. Therefore the main reason for ensuring sufficient facilities to carry out the production plan is to prevent delays in the critical path of portfolio development. Lack of early stage manufacturing facilities in portfolio development may cause multiple projects queuing for the same facility. Simulations with full portfolio candidate products were performed to test the optimal setup of early stage manufacturing capacities. In Figures 4.7 and 4.8, the impacts of changing the capacity available for pre-clinical and for Phase I & II production are displayed in terms of shifts in the out-of-pocket costs on the development timeline. By changing the capacity dedicated to pre-clinical manufacturing from one to two facilities, the finishing times of all pre-clinical and clinical stage development activities are advanced by 1 year, and more importantly the final time to market of successful products is advanced by 1 year as well. Increasing the capacity from 2 to 4 facilities shows no improvement in terms of the products' year of market entry. Nevertheless, using 3 facilities instead of 2 for pre-clinical production does shorten the length of pre-clinical stage and possibly enables the IND submission to occur 1 year ahead (Figure 4.7). Hence the optimal setup of pre-clinical manufacturing capacity should be between 2 and 3 facilities.

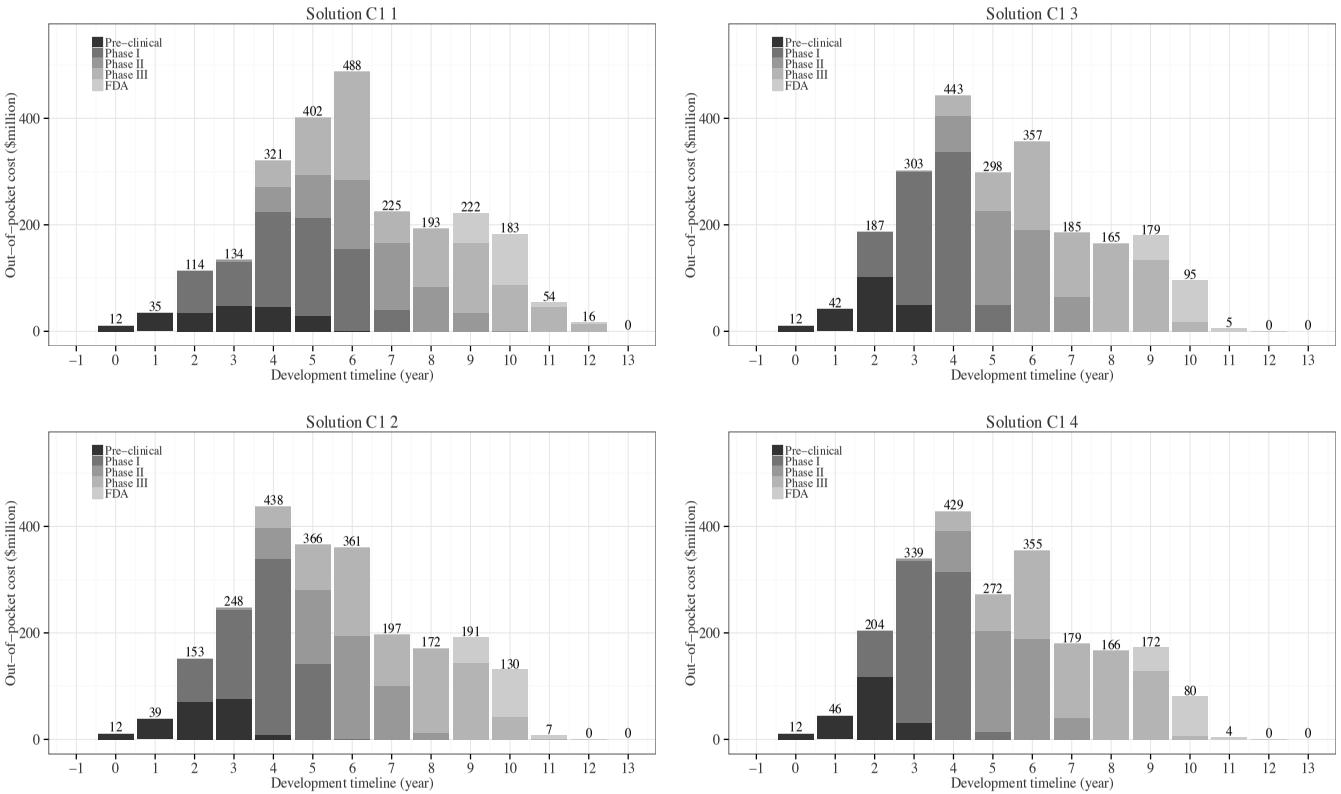


Figure 4.7 Cost distributions on development timeline for full portfolio candidates with number of facilities dedicated for pre-clinical manufacturing ranging from 1 to 4.

All 30 product candidates are selected and the associated cost distribution simulated with different number of facilities available for pre-clinical manufacturing. 1000 Monte Carlo simulations were performed in order to achieve the average out-of-pocket cost for each development stages presented on the timeline. The development stages are highlighted in different degree of grey. For each year, the total annual out-of-pocket cost is displayed on top of the bars. The title for each graph indicates the pre-clinical facility scenarios, e.g. ‘C1 3’ means 3 facilities dedicated for pre-clinical manufacturing.

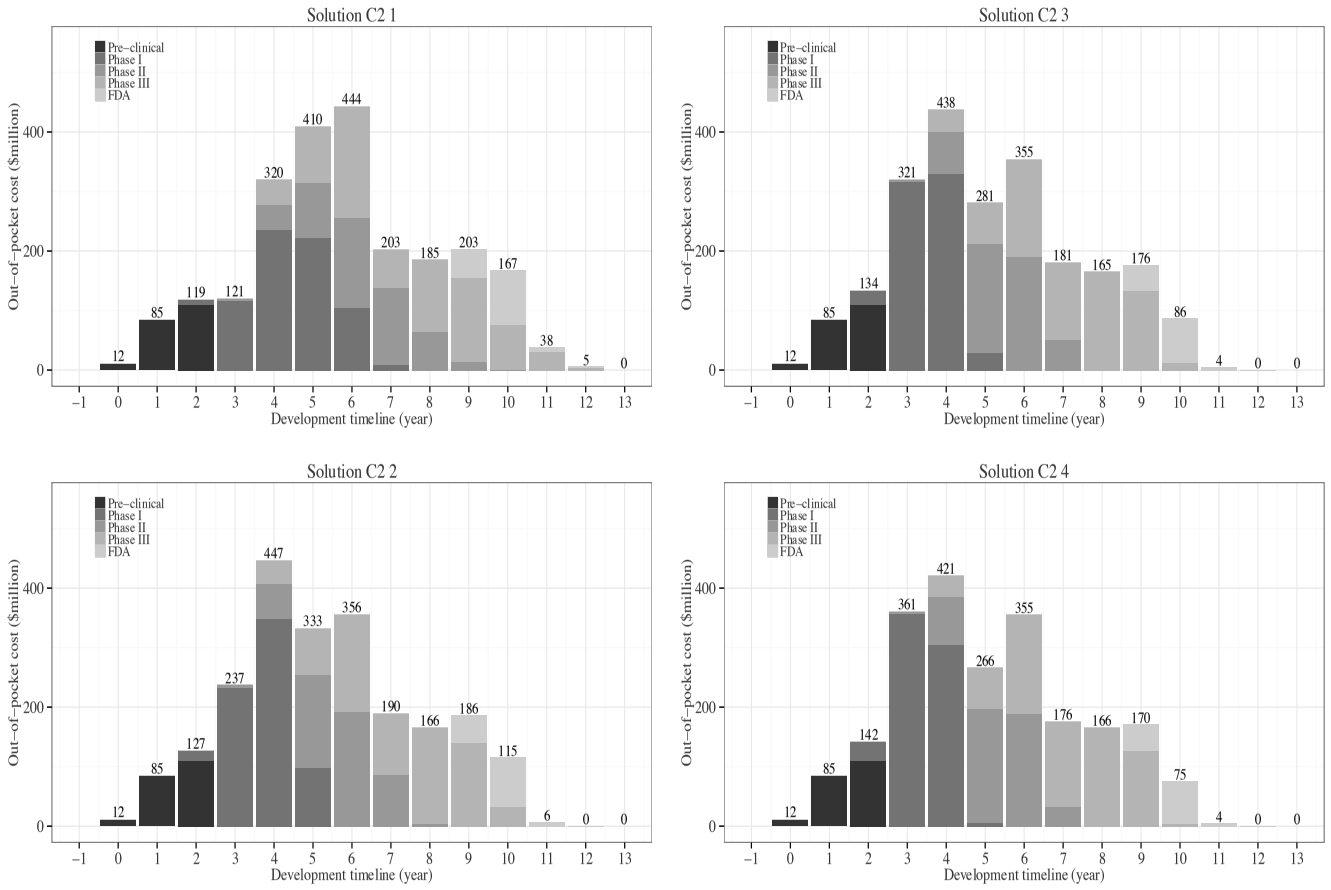


Figure 4.8 Cost distributions on development timeline for full portfolio candidates with number of facilities dedicated for Phase I and II manufacturing ranging from 1 to 4.

All 30 product candidates are selected and the associated cost distribution simulated with different number of facilities available for Phase I and II manufacturing. 1000 Monte Carlo simulations were performed in order to achieve the average out-of-pocket cost for each development stages presented on the timeline. The development stages are highlighted in different degree of grey. For each year, the total annual out-of-pocket cost is displayed on top of the bars. The title for each graph indicates the Phase I and II facility scenarios, e.g. ‘C1 3’ means 3 facilities dedicated for Phase I and II manufacturing.

Phase I & II manufacturing tasks takes longer (10 weeks) per investigational product than pre-clinical manufacturing (6 weeks). The improvements of finishing times due to the transition from one to two facilities are 2 years (7^{th} year to 5^{th} year) and 1 year (9^{th} year to 8^{th} year) ahead for Phase I and Phase II, respectively (Figure 4.8). Increasing capacity from 2 facilities does not lead to significant improvement on the timing of major development milestones, nor does it advance the products' market entry. Therefore the optimal setup of capacity for Phase I & II manufacturing should be 2 facilities.

For Phase III and commercial production, the capacity decision not only determines the timing of clinical trials, but also the profitability of products once they enter the market. Lack of production for commercial purposes may force the drug developers to seek external capacity, which in this case study scenario, is more expensive than in-house production. On the other hand, building a facility for Phase III and commercial scale production is a major investment that will potentially cost the drug developers hundreds of millions of dollars. The trade-off between building in-house facility versus seeking outside capacity exists, especially when the required target amount of production is uncertain. Simulations of portfolio development under uncertainty were implemented to uncover the risk-reward characteristics of solutions under various capacity scenarios. An evolutionary algorithm was applied to the solution pool in order to explore the optimal combination of products for a given capacity constraint. For each capacity setup, the optimal solutions are displayed in the form of a Pareto front.

Figure 4.9 highlights that from 120kg/year to 360kg/year, the performance of Pareto fronts improves significantly. However, the rate of improvement diminishes rapidly above the 360kg/year level (83% coverage of the all-candidate portfolio market potential). Therefore, aiming at around 80% coverage of all candidate projects can be used as a simple rule when encountered with capacity planning decisions.

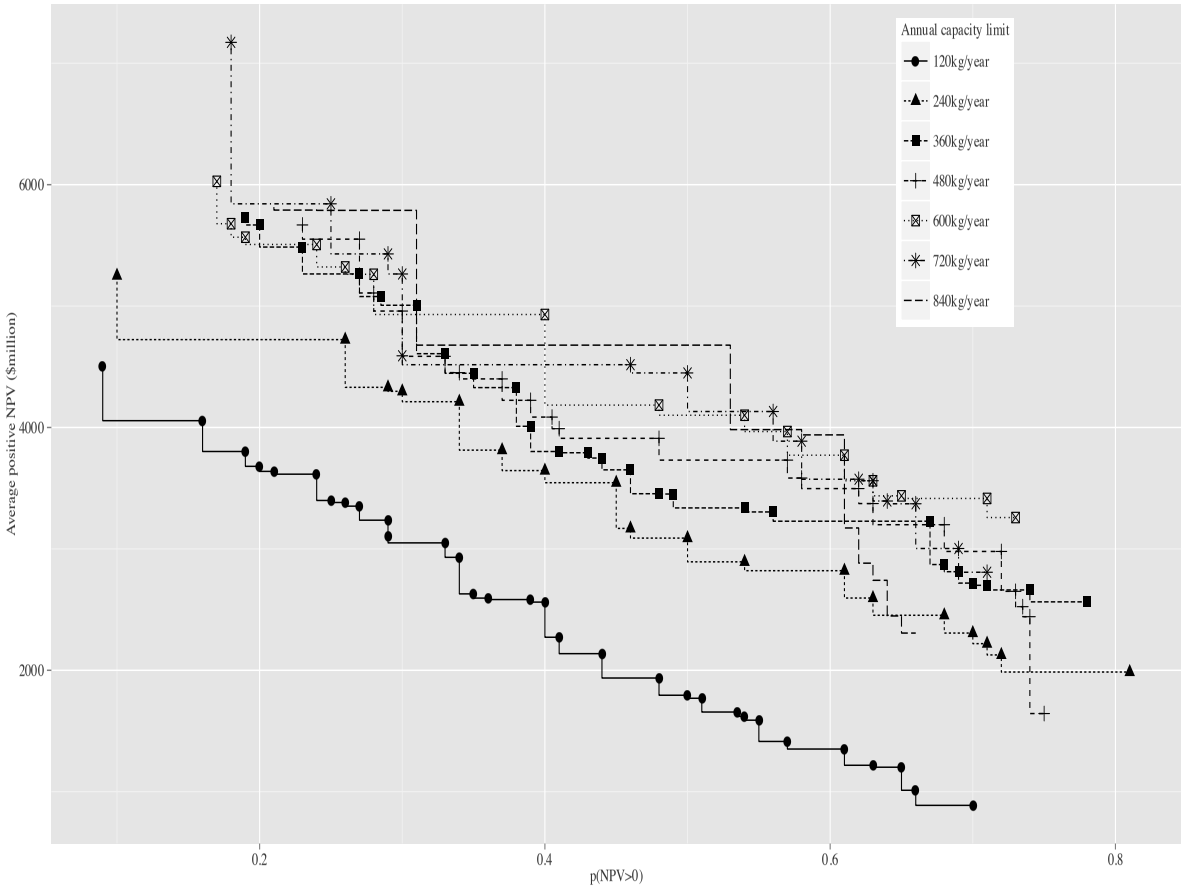


Figure 4.9 Pareto optimal front for solutions under capacity constraints from 120kg/year to 840kg/year.

All the solutions here are results of evolutionary algorithms running for multiple times under various capacity constraints. For each capacity constraint, 50 independent solutions are randomly selected as the initial generation and then processed through 80 generations in order to find the Pareto optimal solutions. For each solution, 100 Monte Carlo trials are performed addressing the random factor in the evaluation model, generating a distribution of NPVs representing the risk-reward characteristics of this solution. With the percentage of positive NPV p(NPV>0) as the measure of risk (the lower the risker) and average positive NPV as the measure of reward (the higher the better), the generation evolves for 30 independent times for each capacity scenarios. This figure presents the final selections of Pareto optimal solutions with x-axis representing the risk measure and y-axis representing the reward measure. In general, in this figure, the Pareto front of higher capacity dominates the one of lower capacity.

From 120kg/year to 360kg/year, the selection towards projects from distinct risk-reward groups drives the shift from high-risk, high-reward region to low-risk, low-reward region. Figure 4.10 depicts the Pareto optimal fronts of 120kg/year, 240kg/year, and 360kg/year constraints from the selection point of view. Overall, the increase in p(NPV>0) is determined by the increase in total number of projects selected, and projects with medium-risk, medium-rewards turn out to be the backbone behind the transition in all 3 scenarios. The selection of low-risk, low-reward projects remains low for the 120kg/year constraint, but increases in number when p(NPV>0) increases under the constraints of 240kg/year and 360kg/year. For the high-risk, high-reward projects, they are less likely to be selected in the 120kg/year scenario when p(NPV>0) increases. The frequency of selection of these projects remains constant in the 240kg/year and 360kg/year scenarios.

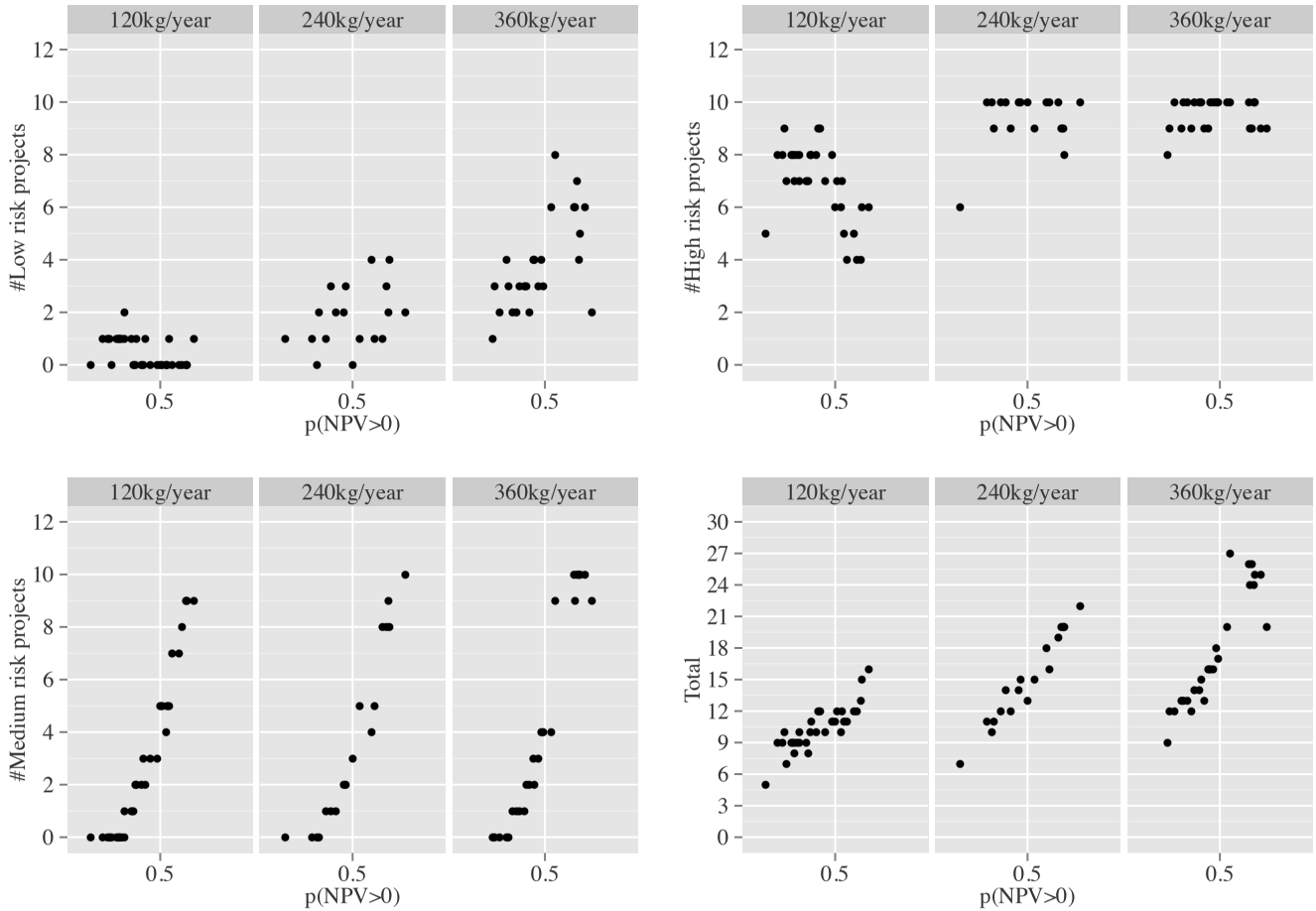


Figure 4.10 Selections toward low, medium, and high-risk and market projects from solutions under capacity constraints from 120kg/year to 360kg/year.

The solutions from Pareto optimal front of 30 independent evolutionary algorithms were aligned based on their p(NPV>0) performances and

Moving from 480kg/year to 840kg/year, the capacity constraint begins to lose its impact on the performance of the drug development portfolio. Solutions from Pareto fronts were aggregated based on their p(NPV>0) values into 3 categories: 0.2~0.4 (high-risk), 0.4~0.6 (medium-risk), and 0.6~0.8 (low-risk). Unpaired t-tests were performed on the solutions from the same risk category to confirm the impact of capacity constraints on average positive NPV. As shown in Table 4.4, in the medium-risk region, there is no significant difference of average positive NPV except when the capacity increases from 600kg/year to 720kg/year. In the low-risk region, the only significant difference exists between the capacities of 480kg/year and 600kg/year. The non-significant differences in risk-reward performances under these capacity constraints can be attributed to the cost of acquiring the capacity units ($88 million per unit). Therefore, the benefit of increasing annual production capacity drops significantly after the 360kg/year capacity level, hence the paramount need for having at least 360kg/year production capacity under the current configuration of the candidate pool.

Table 4.4 P-values between average positive NPVs of solutions from various capacity constraints separated by their p(NPV>0) performances.

Medium risk region	480kg/year	600kg/year	720kg/year
600kg/year	0.2104		
720kg/year	0.0001633	0.009213	
840kg/year	0.0001058	0.005385	0.7344
Low risk region	**480kg/year**	**600kg/year**	**720kg/year**
600kg/year	0.01282		
720kg/year	0.02918	0.8204	
840kg/year	0.5645	0.3096	0.3977

Pareto optimal fronts of scenarios with capacity constraints from 480kg/year to 840kg/year were divided based on their p(NPV>0) into low-risk (0.2~0.4), medium-risk (0.4~0.6), and high-risk (0.6~0.8) regions. The average positive NPVs of solutions from the same region were tested for impact of changing capacity using unpaired 2-tailed student t-test. Significant results from a single incremental of capacity constraint are highlighted.

4.5 RESULTS: CANDIDATES WITH VARIOUS STARTING STAGES

In the case study presented in this subsection, a more realistic scenario of product candidates is designed so that not every product starts at the pre-clinical stage. For the products with higher risk, they are also more advanced in the development pathway. Table 4.5 depicts the changes made to the candidate pool, including the addition of upfront costs for the more advanced products.

Table 4.5 Starting stage, risk profile, market value, and upfront costs for candidates from a more realistic scenario.

Risk profile	Starting stage	% to market	Post-launch NPV ($million)	Upfront cost ($million)
Low	Pre-clinical	21	1500	0
Medium	Phase II	21	5200	25
High	Phase III	19	21000	35

The risk profiles and market values of candidates are the same with the previous study. In this study, it is assumed that all low risk candidates are in-house without any upfront cost to develop. The upfront costs of the more advanced candidates from medium and high risk groups are from Anon. (2013).

To effectively limit the decisions towards the product candidates, budget constraints specifically focused on upfront purchases were introduced. The drug developers cannot make an upfront purchase of candidates worth more than $105, $350, and $600 million, which is equivalent to 3 high risk products, 10 high risk products, and all the medium and high risk products (unlimited), respectively.

The introduction of upfront budget limits has impact on the performances of best solutions. From Figure 4.11, the reward changes significantly when raising the limit from $105 million to $350 million or remove the limit. However, the improvement from $350 million to unlimited upfront budget is not as significant as the one from $105 million to $350 million.

The limitation of $105 million upfront budget prevents the Pareto front from exploring the high p(NPV>0) region by massively in-licensing high market value Phase III products. With $350 million and an unlimited budget for upfront purchase, the Pareto fronts stay in the p(NPV>0) >0.8 region.

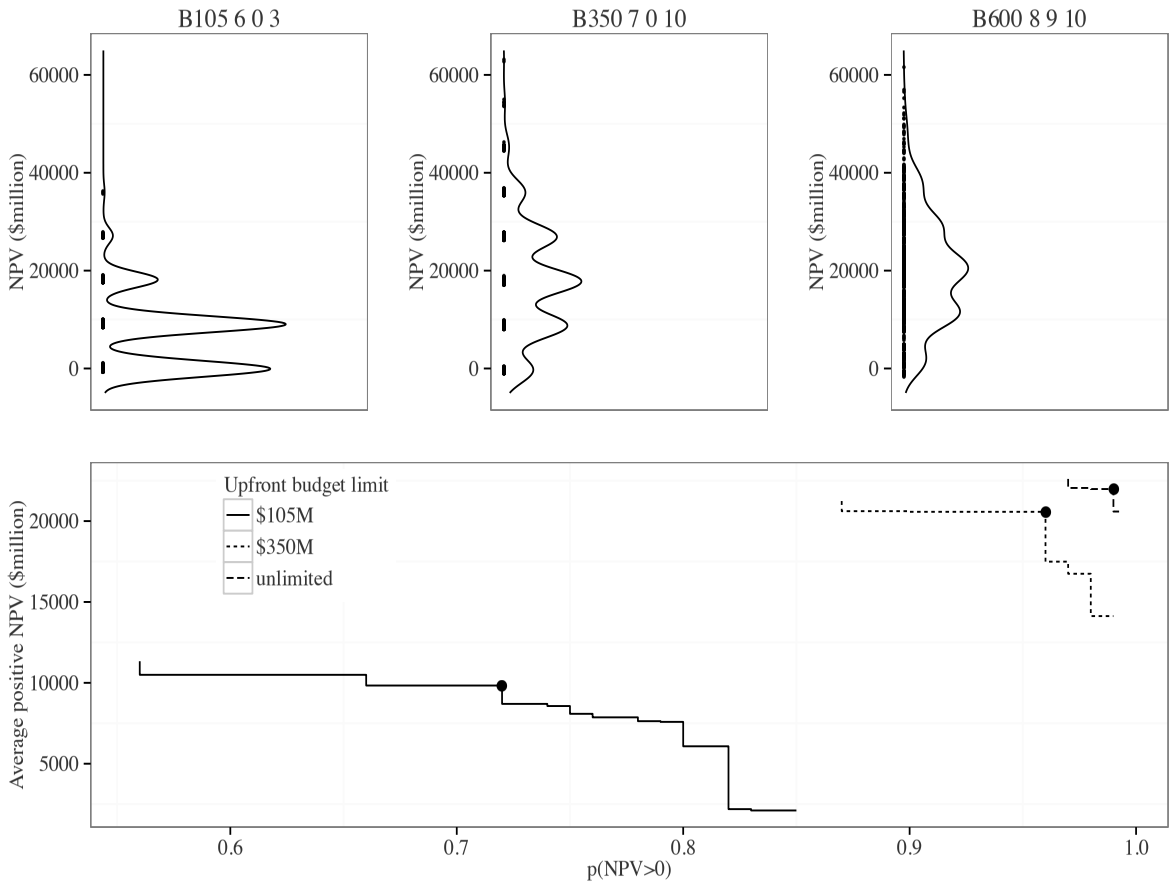


Figure 4.11 Attainable surfaces of Pareto optimal fronts for candidates with different starting stages under upfront budget limits.

Evolutionary algorithm is applied to efficiently searching the decision space under budget limits of $105, $350, and $600 million (unlimited) for optimal portfolio selection combinations. The candidates start from different stages and upfront costs are required to select the more advanced products, therefore compensating their development efforts. The algorithm processed a generation containing 80 randomly generated solutions for 50 evolving generations. Combining 30 independent such processes for each constraint scenario, this figure shows the Pareto optimal fronts of optimal solutions of these problem with x-axis the risk measure represented by the probability of achieving positive NPV and y-axis the reward measure represented by the average positive NPV in $million. Distributions of NPVs from typical Pareto optimal solutions are highlighted in the 3 sub-graphs above, featuring solutions from $105, $350, and $600 million upfront budget constraint with distinct risk-reward performances.

The distribution of NPVs of solutions from Pareto optimal fronts unveils the possible outcomes of portfolio development. With limited budget for purchasing late-stage projects, the distribution of NPVs is largely determined by the success of a few key products, showing a disconnected distribution of NPVs. With the addition of the more reliable medium and late-stage projects, the distribution of NPVs becomes more continuous, reflecting a more steady performance.

Selections from Pareto optimal fronts of various upfront budget constraints reflect the function of product candidates from distinct groups. Under the $105 million limit, the low-risk, early stage, upfront free products drives the increases of p(NPV>0). With higher budgets for upfront payment, the algorithm selects solutions that take advantage of the late stage, high market value products.

A trade-off between the products starting from Phase II and the ones starting from Phase III exists in $105 million budget Pareto front in the transition from high-reward, high-risk region to low-reward, low-risk region. With unlimited budget for purchase, the Pareto front converges into picking all the high market value Phase III products.

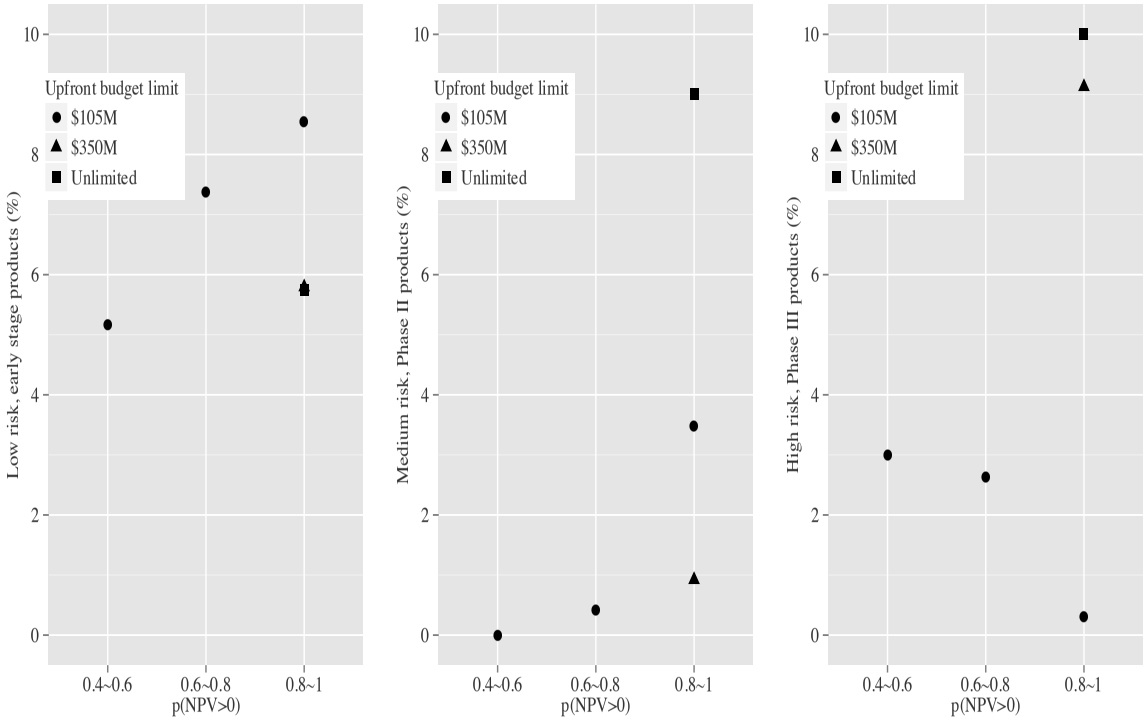
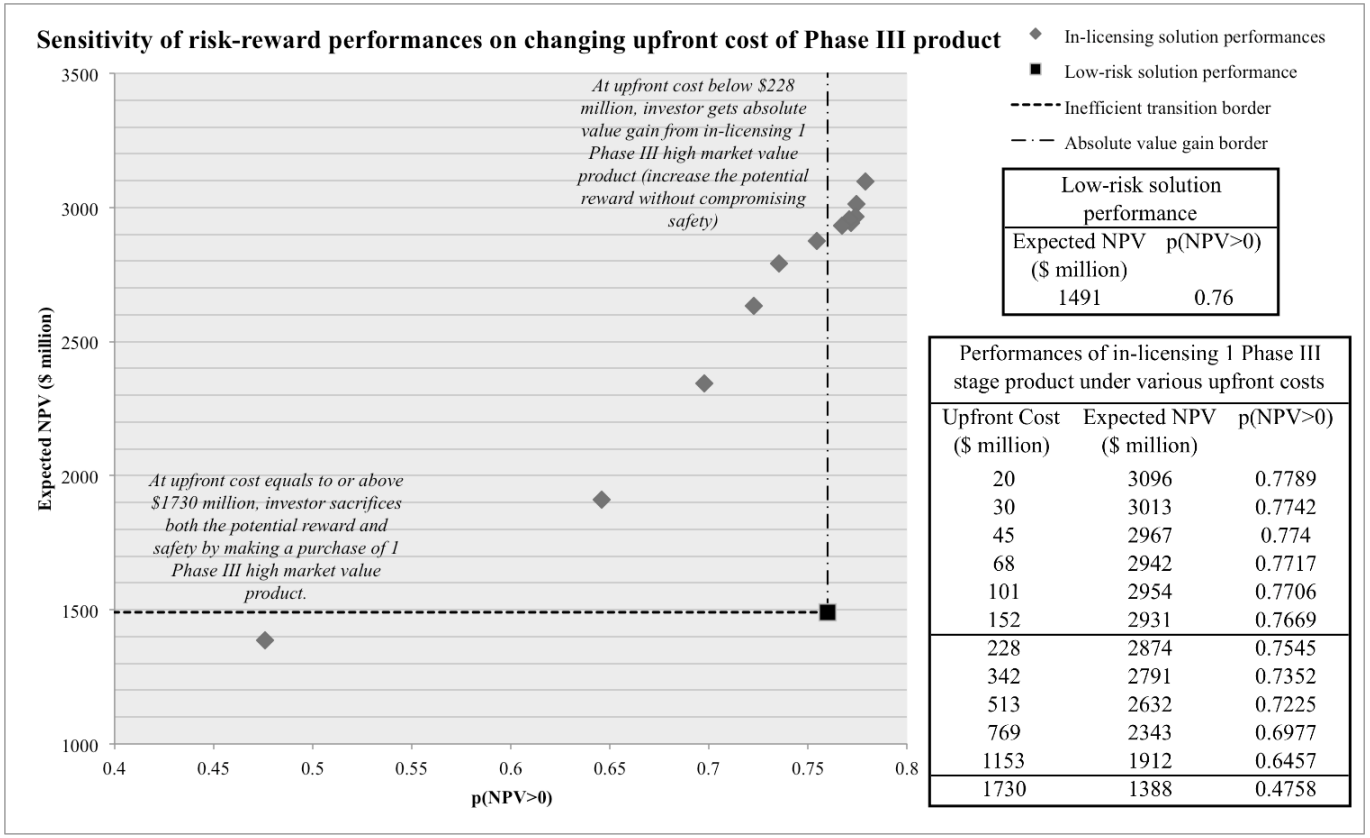


Figure 4.12 Aggregated numbers of selections between low, medium, and high-risk products on all Pareto fronts.

Evolutionary algorithm is applied to efficiently searching the decision space under budget limits of $105, $350, and $600 million (unlimited) for optimal portfolio selection combinations. The candidates start from different stages and upfront costs are required to select the more advanced products, therefore compensating their development efforts. The algorithm processed a generation containing 80 randomly generated solutions for 50 evolving generations. This figures combines 30 independent Pareto fronts for each scenario, and aggregate the percentages of selections towards low, medium, and high risk products based on the solutions' risk performances in p(NPV>0) value 0.4~0.6, 0.6~0.8, and 0.8~1 groups. No data points from the $350 million and unlimited upfront budget scenarios in the first 2 groups since all solutions yield >0.8 in p(NPV>0) performance.

Based on this analysis, the decision-maker can adjust the portfolio risk-reward preference by switching products from different groups when under constraint. However, the optimization results are contingent on the accuracy of model inputs, which can be difficult to achieve. By using the evaluation engine on optimal solution alone, the effect of inaccurate or uncertain inputs can be measured.

Additionally, the acceptable upfront costs when in-licensing projects under portfolio perspective can be explored. From the same starting point of 9 early stage, low-risk projects, 4 Phase II, medium-risk projects, and 0 Phase III, high-risk projects, the tool evaluates the results of performance change when 1 Phase III project is in-licensed. Figure 4.13 shows the possibility of having inefficient transition through the in-licensing deal or gaining absolute value based on different upfront costs. When the upfront cost is under $152 million, the in-licensing deal improves the portfolio performance in terms of both the p(NPV>0) and the expected NPV. Between $228 million and $1153 million, the deal results in mutually non-dominated performance with the original state, sacrificing p(NPV>0) in exchange of expected NPV. When the upfront cost is $1730 million or more, which represents the expected NPV of this single project, the deal turns out to be inefficient as it results in a reduction in both aspects of performance.



Low-risk solution performance	
Expected NPV ($ million)	p(NPV>0)
1491	0.76

Performances of in-licensing 1 Phase III stage product under various upfront costs		
Upfront Cost ($ million)	Expected NPV ($ million)	p(NPV>0)
20	3096	0.7789
30	3013	0.7742
45	2967	0.774
68	2942	0.7717
101	2954	0.7706
152	2931	0.7669
228	2874	0.7545
342	2791	0.7352
513	2632	0.7225
769	2343	0.6977
1153	1912	0.6457
1730	1388	0.4758

Figure 4.13 Sensitivity of risk-reward performances on changing upfront cost of Phase III product.

Evaluations of in-licensing 1 Phase III projects from the existing portfolio composition solution (9 early stage, low-risk products, 4 Phase II, medium-risk products, and 0 Phase III, high-risk products) under various upfront cost were performed in this tool. The resulting performances were divided into 3 categories: 1) absolute value gain, the deal leads to improvement on both performance aspects; 2) non-dominated transition, the deal sacrifices p(NPV>0) in exchange for gain from expected NPV; 3) inefficient transition, the deal causes loss on both performance aspects.

4.6 CONCLUSION

The stochastic optimization tool for biopharmaceutical portfolio management decision-making proposed in Chapter 2 was implemented this chapter. Case studies focusing on portfolio management decision-making and its interactions with budget and capacity resource constraints were formulated and the results discussed. The setup of biopharmaceutical product candidate pool took shape from the cost benchmarks produced in Chapter 3, and the combinations of products from distinct risk-reward characteristics were discussed based on the results of optimization under constraints of various levels. The capability of the activity-based, object-oriented drug portfolio development model was illustrated, and in particular, the information within the data reports regarding the cost distribution across development stages and activity categories was visualized. Therefore this stochastic optimization tool is able to assist the decision maker by offering the option to implement the optimal solutions with detailed planning of budget and manufacturing capacity.

The design of the tool allows more flexibility be introduced in formulating a diversified candidate pool, in which not all products are from the same starting stage. A mechanism relating to in-licensing a product was integrated by factoring in the upfront costs for the more advanced products. Budget constraint on the maximum upfront payment was designed so that the selections between the more advanced, high market potential, outside products and the less advanced, low market potential, in-house products can be in conflict, and therefore optimization of strategy was required. The performances of solutions from Pareto fronts of optimization under different upfront budget constraints are not comparable, as the Pareto front of high upfront budget completely dominates the one of lower upfront budget. Finally, the evaluation engine was utilized for determination of critical transition boundaries when in-licensing products from in portfolio development context. The product's upfront cost is key to distinguish

whether an in-licensing deal leads to absolute portfolio value gain or inefficient transaction.

CHAPTER 5

DRUG DEVELOPMENT LIFECYCLE COST MODEL IN PRACTICE: AN APPLICATION TO CELL THERAPY PRODUCTS

5.1 INTRODUCTION

The drug development lifecycle cost model introduced in Chapter 3 is a general-purpose model for all pharmaceuticals that have similar development patterns. The cell therapy industry (CTI) is a fast growing field that could potentially treat millions of patients and generate revenues in the magnitude of tens of billions over the next decade. The stages in the development cycle for cell therapy products are similar to those for pharmaceutical products in general, with clinical trials on the critical path and non-clinical activities to support the progression of clinical trials. However, there are significant differences in the size of clinical trials and the success rates. In addition, cell therapy products require different manufacturing processes to biopharmaceuticals given that living cells are the final product. The manufacturing of cell therapy products follows a different process and hence requires different cost calculation methods. Given these differences, the benchmark cost evaluation in Chapter 3 developed for biopharmaceuticals needs novel features to be incorporated for applying to cell therapy products with their specific development characteristics. In this chapter the development specifics of cell therapy products are addressed and the drug development lifecycle cost model is implemented to characterize the cost of cell therapy product portfolios. The drug development costs for cell therapies are compared to biopharmaceuticals, focusing on the differences in the total cost and non-clinical cost ratios. This chapter also extends the analysis of how delays in development impact the decision-making by capturing the potential revenue loss.

This chapter is structured as follows. Section 5.2 provides a brief description of the cell therapy product development lifecycle, with emphasis on its specific phase transition probabilities and clinical trial size. The estimation of the market potential of cell therapy products is discussed in Section 5.3. The cost evaluation of developing a single cell therapy product is presented in Section 5.4 with a comparison to biopharmaceutical products. In Section 5.5 an analysis of the costs for developing a portfolio is discussed as well as the impact of delays on potential market revenue loss.

5.2 DEVELOPMENT OF CELL THERAPY PRODUCTS

5.2.1 Development lifecycle description

The development process of cell therapy products follows the same stages as biopharmaceutical products, as described in Chapter 3. In a nutshell, the clinical trials from Phase I to Phase III form the critical path of development, with timely scheduled non-clinical activities, i.e. manufacturing and process development, providing support for trial progression and eventually commercial launch. These non-clinical activities are scheduled such that the clinical trials on the critical path suffer no delay, therefore minimizing the time to market. This inevitably leads to the fact that part of, or the entire non-clinical activity for a given development stage takes place without knowing whether the clinical trial that it underpins will commence or not. With a potential possibility of failure in clinical trials, the manufacturing and process development activities are actually running “at-risk”.

Apart from maintaining these important assumptions about the product development cycle, changes have to be made when applying the drug development lifecycle cost model to cell therapy products. Firstly, the scope of development stages in this study focused on Phase I to FDA review and preclinical trials were not included given insufficient data at this point to estimate the cost components with confidence. Users of this tool can easily change this assumption as more information becomes available.

Secondly, the method of producing material for clinical trial supply is different from protein-based biopharmaceuticals. Therefore a different process economics model was required to capture the cost of manufacturing. Instead of using a product mass-based calculation, the cell therapy product manufacturing target is characterized by the number of cells required. In this study, a UCL process economics model (Simaria et al. 2014; Hassan et al. 2014a) was used to estimate the cost of a cell therapy manufacturing process featuring 10-40 layer cell factories (CF-10 & CF-40) for cell expansion followed by tangential flow filtration (TFF) for volume reduction and washing and finally fill-finish.

Finally, data was collated to estimate the clinical trial success rates and clinical trial patient population sizes for cell therapy products that differ from general pharmaceuticals or biopharmaceuticals. This is discussed in detail in the following sections.

5.2.2 Phase transition probabilities

According to the FDA, "cell therapy products include cellular immunotherapies, and other types of both autologous and allogeneic cells for certain therapeutic indications". This study focuses on allogeneic cell therapies (universal donor) that have a similar business model to biopharmaceuticals that is product-driven rather than service-driven, provides off-the-shelf products and can benefit from scale-up. Examples of approved allogeneic cell therapies include Prochymal (Osiris) for GvHD and Cartistem (Medipost) for osteoarthritis.

Cell therapies are considered to be specific due to the cell types introduced and do not directly interfere with other physiological functions. Small molecule therapies, on the other hand, are generally considered less specific. They may interfere with multiple targets simultaneously, which likely results in higher toxicity and lower efficacy. Therefore, for the purpose of this analysis on cell therapies, clinical trial success rates for large molecule therapeutics provide a more relevant scenario than those for small molecule

therapies. A recent study on pharmaceutical clinical trials shows that for large molecules, the phase transition probabilities for Phase I, II, III, and FDA review are 66%, 38%, 60% and 89% (Hay et al. 2014). Table 5.1 summarizes various sources for biological and pharmaceutical product phase transition probabilities.

Table 5.1 Phase transition probabilities for biopharmaceutical and pharmaceutical products

Phases	I	II	III	FDA	PhI LOA[a]	PhI N[b]
Large molecules (Hay et al. 2014)	66%	38%	60%	89%	13%	7.5
Biopharmaceutical (DiMasi et al. 2010)	84%	53%	74%	96%	32%	3.2
Pharmaceutical & biopharmaceutical (Paul et al. 2010)	54%	34%	70%	97%	12%	8

a. Likelihood of approval (LOA) for Phase I products.
b. Expected number of products (N) in Phase I to achieve 1 approval.

5.2.3 Number of patients in clinical trials

Compared to most pharmaceutical and biopharmaceuticals, cell therapy products typically have much fewer patients in the clinical trials, especially for Phase III. Based on a study summary of 8386 on-going US regulated clinical trials, it can be calculated that the average number of subjects per trial for Phase I, II, and III is 42, 102, and 906 respectively (Krall 2009), see Table 5.2.

Table 5.2 Average number of subjects participating on-going US regulated clinical trials.

	Phase I	Phase II	Phase III
On-going US regulated clinical trials	1342	2600	1090
Subjects (million)	0.057	0.266	0.988
Subjects per trial	42	102	906

The total numbers of trials and subjects for Phase I, II, and III are provided by Krall (2009).

A data analysis into 251 clinical trial registry records on cell therapy products shows that the median numbers of patients in Phase I, II, and III are 12, 50, and 208, respectively, fewer than the average numbers of patients for all US regulated clinical trials (Hassan et al 2014b). Considering the distribution of patient numbers is positively skewed and dispersed, it is more appropriate to use the median values than the average values as the standard cell therapy clinical trial patient numbers.

Table 5.3 Cell therapy clinical trial patient number.

	Phase I	Phase II	Phase III
N	90	111	50
Average	17	73	252
SD	13	77	196
Skewness	1.53	3.62	0.93
Median	12	50	208

Source: Hassan et al (2014b). Data compiled from US clinical trial registry. N – sample size. SD – standard deviation.

The differences in clinical trial enrolment can affect the overall clinical trial cost, assuming the cost per patient remains constant for all products in a given stage.

5.3 MARKET POTENTIAL OF CELL THERAPY PRODUCTS

Sales revenue of product is the most essential way for drug development companies to recover their cost and realise the intrinsic value of products. Quantitative justification for portfolio management decision-making ultimately lies in the profitability indicators such as net present value (NPV). For pharmaceutical products, there are usually large variations in their market potential in terms of annual sales revenue, which makes it difficult to predict the profitability of any particular product. The determinants of sales revenue include therapeutic area, drug pricing, market competition, company's sales force, etc. Empirical studies have been trying to discover the correlations between these determinants and sales revenue with a significantly large sample of marketed products.

However, the purpose for this study is to equip the drug portfolio developers with a tool that conceptually incorporate products' market potential into their decision-making process. This tool establishes the link between portfolio development scheduling decision and its consequences in terms of expected market revenue change. Once the predictions are made on products' market potentials, the decision makers are able to quickly quantify the implications of scheduling decisions on future revenues.

It is therefore appropriate for this study to set the market potential of product on par with some typical marketed cell therapy products in order to provide a more realistic analysis. Dermagraft, a fibroblast-derived dermal substitute for treating chronic diabetic foot ulcers (DFUs), grossed $44 million on its first year of approval by the FDA in 2008, netting $28 million gross profit for its originate company, Advanced BioHealing. The revenue income from Dermagraft continued to grow in 2009 and 2010, with revenues of $85 million and $146 million, and gross profit of $65 million and $115 million (Mason et al. 2011).The sales plunged to $105 million in 2011, when the company is purchased by Shire for $750 million, and rebounded to $153 million in 2012 before Dermagraft was sold to Organogenesis (Shire Plc 2013). Provenge, an autologous cellular

immunotherapy for the treatment of metastatic prostate cancer, brought $48 million revenue for its originating company Dendreon in 2010 when it commenced market sales in May. In the following year it grossed $213 million and $325 million the year after. The sales revenue fell to $284 million in 2013 (DENDREON CORPORATION 2014). Based on sales figures of these industry flagship products, the following assumptions on typical market potential are made.

1. First year revenue is assumed to be $50 million. This is on par with the first year sales of Dermagraft. Provenge's first year sales only account for 7 months in market, therefore the real first year sales will be larger than $50 million. With sales figures conservative assumptions are preferred in this study therefore the smaller one is chosen.
2. Peak sales income is achieved on the 3rd year of market entry. This is true for both of these products. After the 3rd year, the sales fall gradually.
3. The amount of peak sales is $150 million. This is again on par with Dermagraft, which is the smaller of the two selected products.
4. The sales ramp up curve is represented by the annual sales as percentage of peak sales. For this study, the percentages are 33%, 67%, 100%, and 80% from the 1st year to the 4th year of market entry. This is consistent with both products after converting Provenge's 7 months first year sales into effective 1-year sales assuming the sales are proportionate throughout the year. After the 4th year, the sales drop to 50%, 10%, and 0% of peak sales in the 5th, 6th, and 7th year. 6 years of effective market operation of the product is assumed due to the limited length of patent protection.
5. The gross margin for cell therapy product is 65%, on par with the 1st year figures on Dermagraft gross profit. As the sales increase, the gross margin will increase due to the economies of scale. 65% marks the lower limit of cell therapy product's gross margin and is consistent with the conservative principle.

Table 5.4 summarizes the assumptions on market potential of typical cell therapy product in this study. These assumptions are made based on conservative principles, which lead to relatively modest sales figures.

Table 5.4 Market potential of typical cell therapy product.

Year(s) after market entry	1	2	3	4	5	6
% of peak sales	33%	67%	100%	80%	50%	10%
Sales revenue ($million)	50	100	150	120	75	15
Gross profit ($million)	32	65	98	78	49	10

The peak sales of $150 million occur on the 3rd year of market entry. The gross margin for all sales is 65%.

The linkage between development scheduling and product market potential takes into account the effect of competition from either other originators or follow-on biologics. Study shows that in 1990-2003 period there are 30% of follow-on drugs filed the investigational new drug (IND) application prior to the first-in-class compound (DiMasi & Faden 2010). The introduction of follow-on competitions normally accompanies price discounts (Wertheimer et al. 2001). In this study, the effect of market competition is quantified in terms of penalties to the scheduling decisions that results in delay to market entry. In Chapter 4, an assumption was made for biopharmaceutical products that one year's delay to market would lead to a 35% loss of market value, due to the potential damage to the product's competitive position (Kennedy 1997). Since cell therapy products are relatively new and their market potentially less competitive, a moderate assumption was made that for each year of delay, the peak sales of product is reduced by 25%.

5.4 COST OF DEVELOPING A SINGLE CELL THERAPY PRODUCT

5.4.1 Cost of process development

In this study, the cost evaluation of process development activities inherits the framework proposed in Chapter 3, with all pre-clinical tasks transferred

to Phase I. This change does not contradict the assumptions on process development functionality in the previous analysis as there are no Phase I process development tasks assigned. Since the starting point of this analysis is Phase I, it is safe to assume the cost of process development previously assigned to pre-clinical stage transferred to Phase I stage. Table 5.5 presents the result of in-house analysis of cell therapy process development cost and durations. The cell therapy process development activities are divided by function into 4 categories: process optimization, technology transfer, process characterization & validation, and product stability. Compared to biopharmaceuticals, the process development costs of cell therapy products are similar for early stages (Phase I and II), but much lower for late stages (Phase III and FDA review).

Table 5.5 Cost evaluation of process development activities for cell therapy product in clinical trials (Hassan et al. 2014b).

	Phase I	Phase II	Phase III	FDA
Process optimization ($million)	0.5	0.5	1.5	0
Technology transfer ($million)	0.5	0.5	0.5	2
Process characterization & validation ($million)	0	0	0.18	1.9
Product stability ($million)	0.05	0.02	0.01	0
Total cost ($million)	1.05	1.02	2.19	3.9
Duration (year)	0.5	0.5	2	1.5

The process development activities are divided into 4 main functions: process optimization, technology transfer, process characterization & validation, and product stability.

5.4.2 Cost of manufacturing

The typical manufacturing process for cell therapy products involves several key steps that are different from biopharmaceuticals. The cells/tissue must be acquired first for primary cell isolation into master & working cell banks. These cells are then expanded. Harvested cells from these cell cultures go through volume reduction and washing steps in order to properly formulate

the cell therapy product. Cryopreservation is typically used for allogeneic therapies to extend shelf-life, facilitate storage and distribution before they are tested for release to end-user handling. The key technologies in this process are cell factories (CFs) for cell expansion, followed by tangential flow filtration (TFF) for volume reduction and washing. In this study, the facility for production for clinical trial manufacturing is fixed at CF-10 lots for Phase I and II and CF-40 for Phase III with TFF and vialing, with 10^8 cells per dose and 2 doses per patient as treatment. The cost of manufacturing was calculated using a UCL process economics model specific for cell therapy products (Simiaria et al. 2014; Hassan et al 2014a). This model was configured with standard planar technologies throughout the development stages. The key input variable to the model was the target amount of cells to produce and the total cost of goods per batch was the key output used in this study. The cost of goods included direct costs (e.g. materials) and indirect costs such as the capital charge that is a yearly cost that takes into account the FCI, the facility's useful life (10 years), and the interest rate. The capital charge was divided by each manufacturing lot commenced within 1 year. Table 5.6 depicts the flow of calculations for the cell therapy process economics model with the resulting manufacturing cost as output. The number of patients here is adapted from the median values of clinical trial enrolment for existing cell therapy products described in Section 5.2.

Table 5.6 Cost of manufacturing for developing cell therapy product.

Development stage	Phase I	Phase II	Phase III
Optimal technology setup	10 x CF-10 & TFF & vialing	20 x CF-10 & TFF & vialing	8 x CF-40 & TFF & vialing
Dose (cells/patient)	10^8	10^8	10^8
Nr. of doses/patient	2	2	2
Nr. of patients	12	50	200
Nr. of lots per year	3	3	14
Clinical trial duration (year)	1.5	2.5	3
Manufacturing cost ($million)	1.18	2.33	3.25

Note: The patient numbers are assumed to be similar with the median values of clinical trial enrolment for existing cell therapy products.

5.4.3 Cost of clinical trials

The clinical trial activities normally contribute most to the total cost of developing investigational therapeutics. However, in the cell therapy area, due to the lack of systematic study on clinical trial costs, it is unknown what proportion it takes in the total cost of developing cell therapy products. It is therefore inevitable to make assumptions regarding the cost of clinical trials. In this study, the costs of clinical trials per patient are assumed to be consistent for all therapeutic drugs for the same trial, since the variable component of costs of clinical trials depends on the number of patients participating the trial. The cost of hospital and patient recruitment can be considered constant regardless of the product.. The user of this tool can alter this assumption as it only serves to provide realistic input for the tool.

This assumption provides essential link between existing clinical trial cost studies and cell therapy clinical trial costs. In Chapter 3 the number of patient is assumed to be 50, 200, and 2000 for Phase I, II, and III for biopharmaceutical products. Section 5.2 establishes the fact that for cell

therapy products the number of patient enrolment is much smaller. Hence it is safe to say the cost of clinical trials will be lower by a significant margin. The exact estimates of cell therapy clinical trial costs are summarized in Table 5.7, where published total phase costs were used to deduce the cost of clinical trials for pharmaceutical products (Paul et al. 2010). The clinical trials costs for cell therapy products in Phase I and II are ¼ of the costs for pharmaceutical drugs. In Phase III, cost of clinical trial for pharmaceutical products is 10-fold the cost for cell therapy products.

Table 5.7 Cost of clinical trials for cell therapy products.

	Phase I	Phase II	Phase III
Clinical trial cost (pharmaceutical, $million)	14	37	131
Patient number (pharmaceutical)	50	200	2000
Cost per patient ($ thousand)	275	186	66
Patient number (cell therapy)	12	50	200
Clinical trial cost (cell therapy, $million)	3	9	13

Note: The cost per patient is assumed to be consistent regardless of the nature of therapeutic drugs. The cost of clinical trials for pharmaceutical products are derived from published total phase costs less the costs of non-clinical activities (Paul et al. 2010).

5.5 PORTFOLIO DEVELOPMENT COST EVALUATION OF CELL THERAPY PRODUCTS

The drug development lifecycle cost model is implemented with cell therapy product development specific configurations. The results of portfolio development costs are presented for activities across development stages and clinical versus non-clinical categories. Comparisons of cost distributions are made between pharmaceutical, biopharmaceutical, and cell therapy portfolio development. A sensitivity analysis exploring the impact of changing Phase II transition probability is performed, showing that the required number of projects at Phase I and the early stage non-clinical cost

are most affected. Finally, the model investigates the portfolio valuation by constructing cash flows from development stages to market incomes, featuring the scenario analysis where 1-year delay occurs during the Phase III stage.

5.5.1 Cost evaluation

The portfolio development cost evaluation is achieved through model simulation of development activities from clinical trial, manufacturing, and process development. The number of products in the portfolio was configured such that 1 market success can be achieved on average. The drug development lifecycle cost model simulates the development pathway of all these products by deterministically scheduling relevant activities and produces costs distributions across both development stages and activity categories.

Figure 5.1 depicts the cost evaluation of cell therapy product portfolio development targeting 1 market success. The overall cost of developing 1 market successful product on average is $157 million. Dividing the development stages into early stage as Phase I and II, and late stage as Phase III and FDA review, the early stage development costs takes up around 75% of the total cost. The most cost extensive stage is Phase II with $71 million out-of-pocket cost and 35% of which is spent on non-clinical activities, i.e. process development and manufacturing. The ratio of clinical trial costs from early stage to those from late stage is approximately 2.5:1. The total non-clinical is about 37% of the total portfolio development cost across all development stages. The ratio of early stage non-clinical cost to late stage non-clinical cost is 2.5:1. Phase II manufacturing cost tops the non-clinical costs with $17 million, followed by Phase I manufacturing cost of $9 million. The costs of process development remain flat at $7~8 million throughout clinical trial stages from Phase I to Phase III. These cost distribution parameters can facilitate critical budget planning decisions in developing cell therapy products. The distributions of stage costs of each activity categories also reflect the ideal market composition in those

activities, which can be useful for analyzing gaps in existing market composition and discovering opportunities.

Compared to the cost evaluation of pharmaceutical and biopharmaceutical products discussed in Chapter 3, the cost of developing cell therapy product portfolio is considerably smaller. Figure 5.2 presents the comparison of cost distributions of portfolio development of pharmaceutical, biopharmaceutical, and cell therapy products. The phase transition probabilities of pharmaceutical and biopharmaceutical product development are adopted from Paul et al. (2010) as the industrial average benchmark. The cell therapy product phase transition probabilities are represented by large molecule success rates from the study on clinical success rates of investigational drugs (Hay et al. 2014). The benchmark costs of manufacturing for all product categories are from in-house process economics model featuring specifically the material requirements of clinical trials. By analyzing the functional tasks and personnel of process development in each drug development stage, the benchmark costs of process development are produced. The costs of clinical trials for pharmaceutical and biopharmaceutical products are deducted from the published total phase costs (Paul et al. 2010; DiMasi & Grabowski 2007). For cell therapy products, the clinical trial costs are estimated assuming the cost per patient remains constant for a given stage of clinical trial and there are no fixed cost components. The comparison presented in Figure 5.2 shows that the portfolio development cost of biopharmaceutical products is the highest among the three, primarily because of the large amount of spending in Phase I development. Pharmaceutical product portfolio development cost is around the same value, but more focusing on Phase III development. For cell therapy portfolio development, the most cost spent is on Phase II, taking up almost half (~45%) of the total development cost.

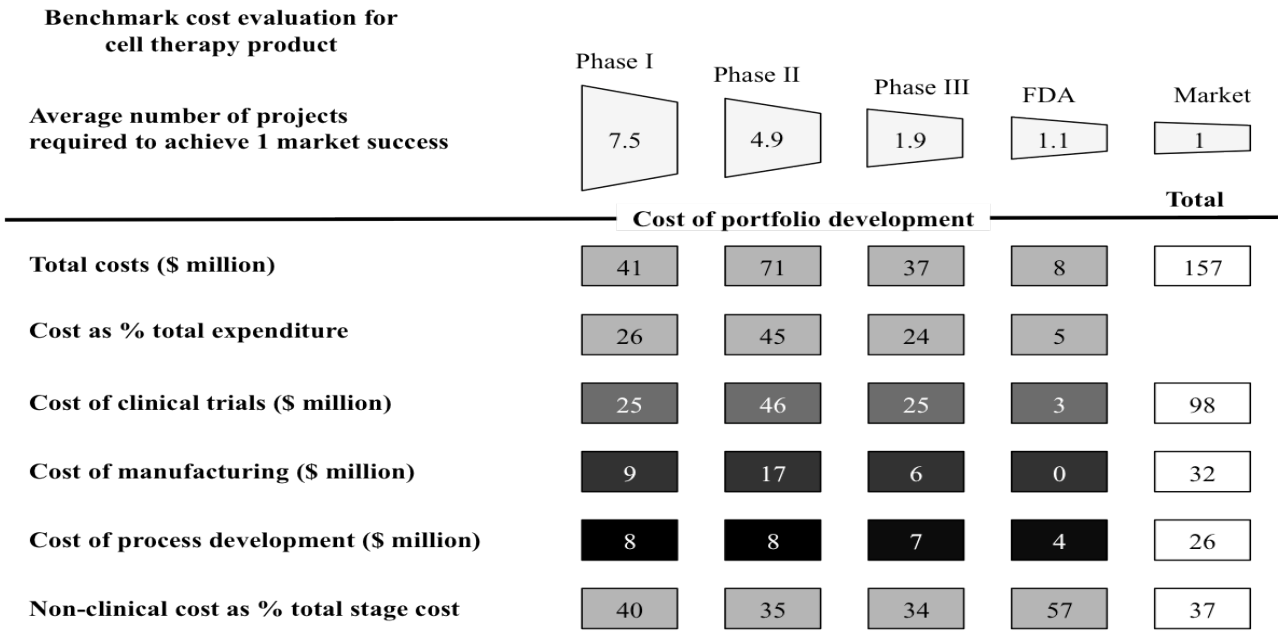


Figure 5.1 Cost evaluation of new cell therapy product development.

The phase transition probabilities adopted in this evaluation are the published values of large molecule investigational new drugs (Hay et al. 2014). The costs of clinical trials are estimated based on the number of patient enrolment and the costs for pharmaceutical products in general. From the phase transition probabilities the average number of projects required to achieve 1 market success at each development stage are calculated. The costs of portfolio development are derived from the numbers of projects required and the costs of developing a single product.

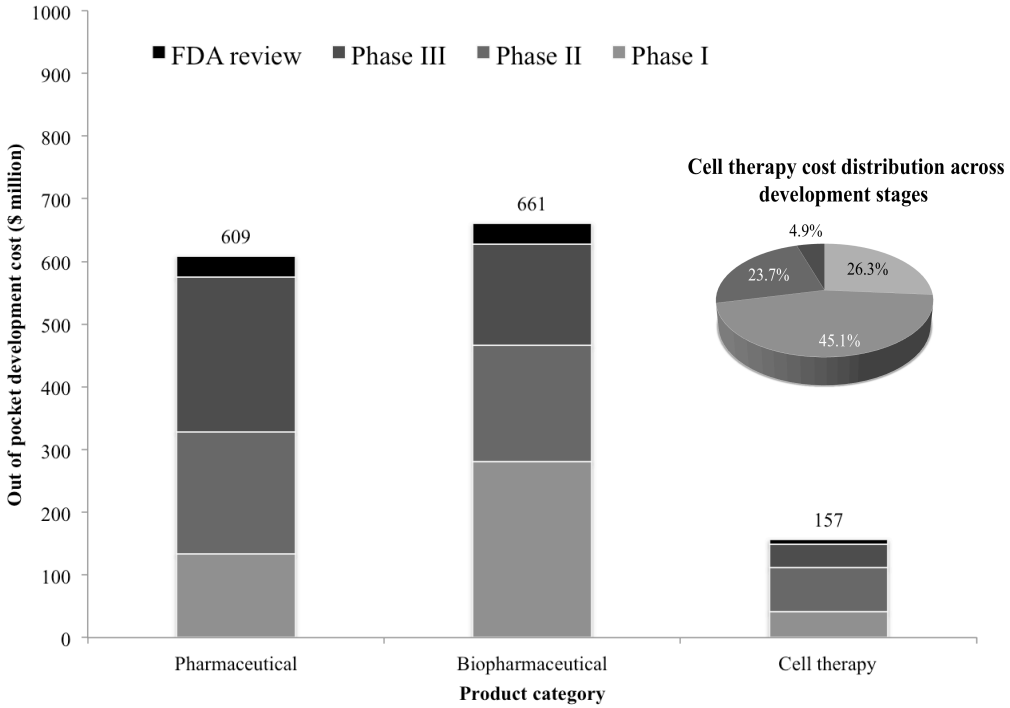


Figure 5.2 Cost distribution across development stages for developing an R&D portfolio targeting 1 market success.

The cost distributions across stages are presented for 3 different product categories: pharmaceutical, biopharmaceutical, and cell therapy products. The pie chart within this figure features the cost distribution across development stages for cell therapy product. These costs are out-of-pocket costs taking into account the costs for failed projects. The total portfolio development cost is on the top of each bar. The costs for pharmaceutical and biopharmaceutical portfolio development excludes the costs spent on pre-clinical stage.

The model also captures the cost distributed to manufacturing and process development activities. Figure 5.3 shows the manufacturing and process development cost distribution across all stages of portfolio development for cell therapy products as well as biopharmaceutical products. The overall cost of non-clinical activities is $58 million for cell therapy product portfolio and $129 million for biopharmaceutical product portfolio from Phase I to FDA review stage. Biopharmaceutical product portfolio development focuses more on FDA review stage process development since extensive process characterization and validation tasks are required to formulate the BLA documentation and the drug developing company also needs to prepare its commercial production. Cell therapy product portfolio,

on the other hand, is much less costly in late stage process development but more expensive in manufacturing to provide materials for Phase II clinical trial as there is quite a significant number for patient enrolment in Phase II. From a budget planning point of view, the transition from biopharmaceutical product portfolio to cell therapy product portfolio implies big cuts in process development costs, especially for Phase III and FDA review stages, and relatively small cuts in manufacturing costs.

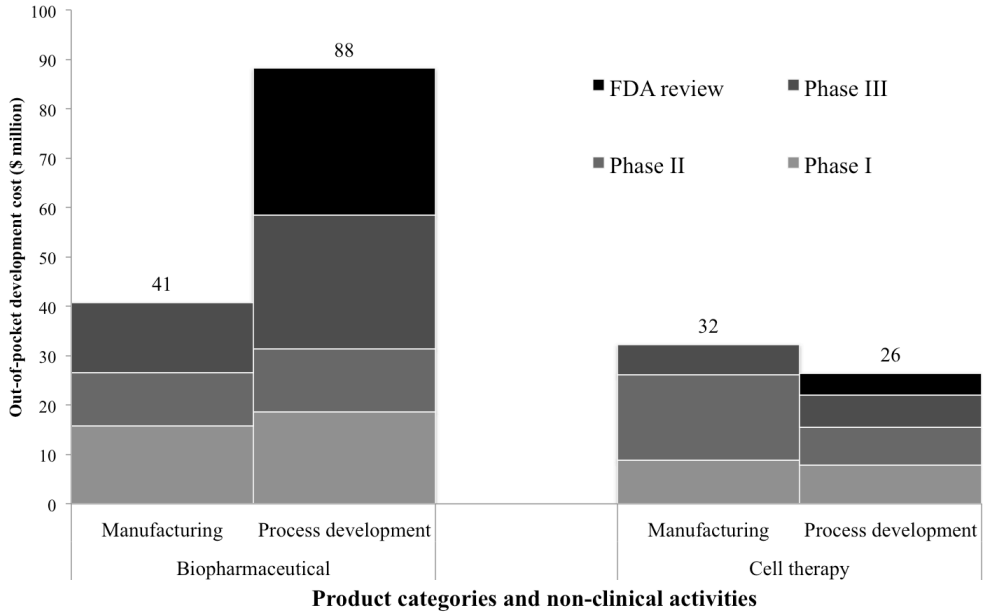


Figure 5.3 Process development and manufacturing cost distributions across development stages for biopharmaceutical products and cell therapy products portfolio targeting 1 market success.

The costs are out-of-pocket costs including the spending on failed projects. The total costs of process development and manufacturing for portfolio development are presented on top of each bar. The process development cost of biopharmaceutical portfolio development in Phase I takes the value of pre-clinical cost as they perform similar functions in the analysis.

A more detailed comparison between biopharmaceutical and cell therapy product portfolio development cost evaluation is presented in Figure 5.4. Evidently it is more than 3 times more expensive to development a successful biopharmaceutical product than a cell therapy product because of 1) the higher attrition for biopharmaceutical projects: 8.6 products are

required at Phase I for biopharmaceuticals compared to 7.5 for cell therapy products; 2) the higher cost of clinical trials across all clinical stages: almost 3.5 (Phase II) to 11 (Phase I) times higher for biopharmaceuticals than for cell therapy products; 3) the higher cost of non-clinical activities: more than 2 times higher in total non-clinical cost for developing biopharmaceuticals than for cell therapy products as described in previous paragraphs. Despite the higher non-clinical costs, the ratio of non-clinical cost against the total cost for biopharmaceutical portfolio development is much smaller than that of cell therapy portfolio, almost half the percentage (19% versus 37%), which suggests that the cell therapy product developer should focus more on non-clinical activities.

		Phase I	Phase II	Phase III	FDA	Total	
Total costs ($ million)	7.5 projects	41	71	37	8	157	Cell therapy
	8.6 projects	281	185	162	33	661	Biopharmaceutical
Cost of clinical trials ($ million)		25	46	25	3	98	Cell therapy
		265	162	121	3	551	Biopharmaceutical
Cost of manufacturing ($ million)		9	17	6	0	32	Cell therapy
		16	11	14	0	41	Biopharmaceutical
Cost of process development ($ million)		8	8	7	4	26	Cell therapy
		19[a]	13	27	30	88	Biopharmaceutical
Non-clinical cost as % total stage cost		40	35	34	57	37[b]	Cell therapy
		12	13	25	90	19[c]	Biopharmaceutical

Figure 5.4 Cost comparisons between cell therapy product portfolio and biopharmaceutical product portfolio development.

The phase transition probabilities for biopharmaceutical products are from Paul et al. (2010) and the total phase costs are from DiMasi & Grabowski (2007). For cell therapy products, large molecule clinical trial phase transition probabilities (Hay et al. 2014) are used and the costs of clinical trials are deducted assuming constant cost per patient. Number of projects required in Phase I to have 1 market success in average is presented, as well as the cost distribution across development stages and activity categories. Non-clinical activities include process development and manufacturing. a) The process development cost for Phase I for biopharmaceutical products takes the value of pre-clinical process development cost as they perform the same function. b) The percentage of overall non-clinical costs over the portfolio development cost. c) For biopharmaceutical products, this percentage takes into account the cost spent on pre-clinical stages.

5.5.2 Sensitivity analysis

Assumptions have been made in the previous analysis of cost evaluation of cell therapy product development since when this study carried out the area was largely unexplored. It is therefore reasonable to test the sensitivities of cost evaluation results against those assumptions in order to obtain a more comprehensive understanding of the implications should those assumptions fail to represent the reality. In this study, the drug development lifecycle cost model is implemented with changing inputs in a one-factor-at-a-time (OFAT) fashion, capturing the percentage deviations of cell therapy portfolio development cost evaluation results.

As the stage that divides early stage and late stage and with the highest likelihood of project failure, Phase II is selected as the research focus in this study. A published research study on success rates of investigational drugs (Hay et al. 2014) shows that variations exist in Phase II transition probability for development of drugs in different therapeutic areas. The range of possible Phase II transition probabilities is from 26% (32% lower than the benchmark input) to 50% (32% higher than the base case input).

Figure 5.5 presents a sensitivity analysis of the portfolio cost determined by the model to the Phase II transition probability as well as other key model variables. In general, the increases in percentage variations of costs from base case are larger than the decreases caused, if changing the Phase II transition probability at the same magnitude. Similar percentage variations appear for projects required at Phase I, the early stage non-clinical cost, and the Phase II stage cost, revealing the fact that the calculation of these parameters follows the same principle of calculating expected values. The model constructs a portfolio based on attrition rates in order to get 1 market success, and works on the cost of activities from each stage by multiplying the cost of that activity with the number of projects required in that stage.

The variations of total clinical trial cost as well as total cost of portfolio development are smaller than the variation of Phase II stage cost, since there is no change in the cost after Phase II, which is part of total portfolio

development cost. However, there is variation for Phase III non-clinical cost as well as its percentage of total phase cost because the non-clinical activities for Phase III actually starts at Phase II stage before the knowledge of Phase II success. Decreasing Phase II transition probability also increases the percentage of early stage cost against total cost, as more projects are required in early stages.

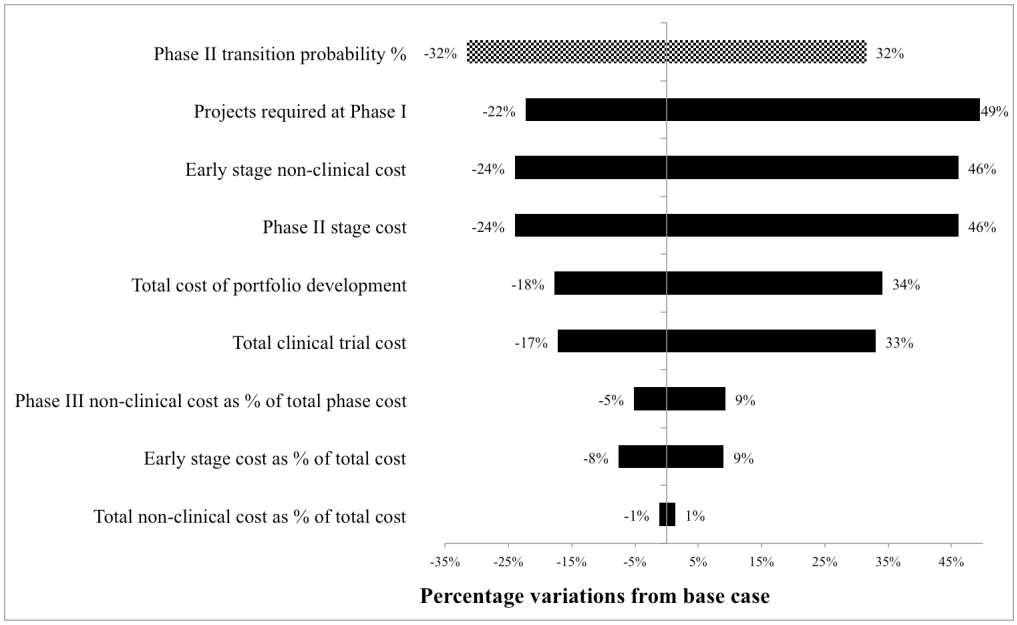


Figure 5.5 Sensitivity analysis on cell therapy cost evaluation results when Phase II transition probability changes.

The Phase II transition probability varies from 38% in benchmark analysis to 26% as the lowest possible value and 50% as the highest possible value for all therapeutic areas. The variations of cost evaluation results are reflected in terms of percentage increases or decreases from the benchmark.

5.5.3 Portfolio valuation and impact of delay to market

The drug development lifecycle cost model is capable of capturing portfolio development timelines and milestones, therefore constructing expected cash flows. With the projections of a product's market revenue and profit margin, the portfolio NPV can be achieved by the discounted cash flow (DCF) method that combines the cash flow generated from cost of development and profit of marketing the product.

Considering the cost of portfolio development as cash outflow or negative cash flow, and the profit from market revenue as cash inflow or positive cash flow, the cash flow chart of developing a cell therapy product portfolio targeting one market success is established in Figure 5.6. For the first 5 years of development, the annual cost of portfolio development is around \$20 million except for the 3rd year where the cost surges to more than \$40 million, which deserves special attention from cell therapy developers as the increased amount of cost could potentially cause delay because of the shortage of development budget. Once after the product's market entry, the drug developer should expect an injection of profit that almost covers all portfolio development cost. Measures should be taken at this point to ensure the level of market penetration that strengthens the sales, and to seek opportunities for making good use of the increased capital.

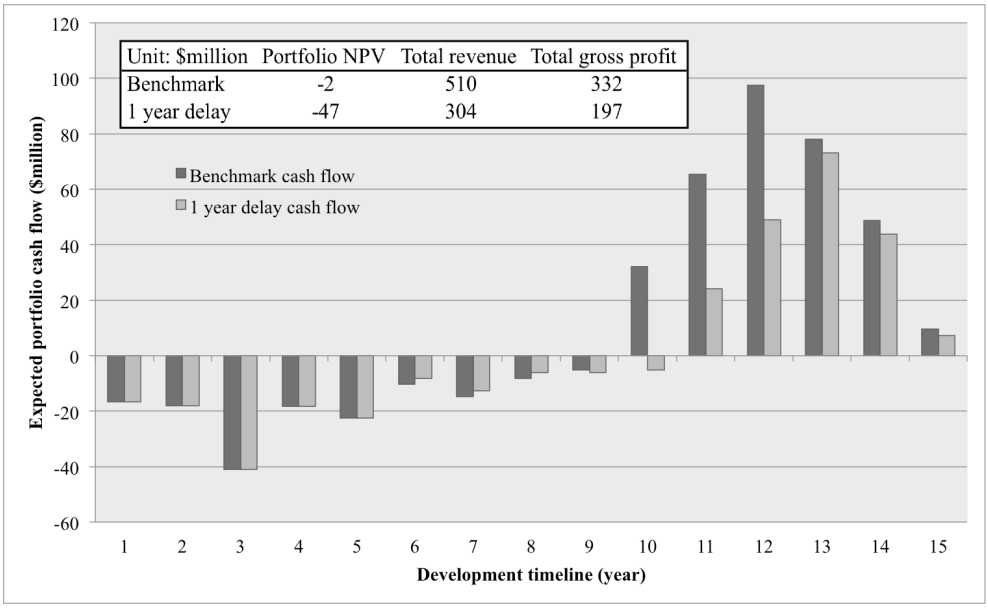


Figure 5.6 Expected cash flows for developing cell therapy product portfolio targeting 1 market success.

The cost evaluation figures are separated by the time of cost incurring. All cost figures are treated as negative cash flow to the drug development company, with all gross profits from marketing the product contributing to positive cash flow. Scenario where 1-year delay occurs in Phase III development stage is analysed and the results presented along with benchmark results. The revenue and gross profit loss due to the increased likelihood of competition after delay are captured. Portfolio NPVs are produced for both scenarios based on a 10% discount factor specific for pharmaceutical industry NPV calculations.

The simulation presented in Figure 5.6 also captures the effect of a 1-year delay in Phase III development. It not only causes the market entry to delay accordingly, but also decreases the peak sales by 75% because of the increased amount of competition introduced by the delay. With the limited time of patent protection, the total market operation time of the product is also reduced, resulting the revenue loss of ~$300 million or profit loss of ~$135 million. From a portfolio NPV perspective, the original development scheduling provides $2 million in negative expected NPV when applying 10% discount rate, which is reasonable considering in this study the more conservative assumptions of product market potential are employed. With the 1-year delay scenario, the portfolio expected NPV drops to negative $47 million, which will not be tolerable to most decision makers.

5.6 CONCLUSION

In this chapter, the drug development lifecycle cost model was implemented to benchmark the cost of developing cell therapy product portfolio aiming at 1 market success. The costs of clinical trials, manufacturing, and process development across the development lifecycle of cell therapy product were estimated in a single product basis as inputs to the model. The cost evaluation of portfolio development resulted in a total out-of-pocket cost of $157 million per successful cell therapy product. Results of pharmaceutical and biopharmaceutical portfolio development cost evaluations were compared with cell therapy products, emphasizing the cost features of non-clinical activities and their proportions to the total portfolio development cost. A sensitivity analysis investigating the impact of changing Phase II transition probability on the evaluation results was presented, revealing key mechanisms of the cost evaluation process and the magnitude of possible variations. Finally, an analysis utilising the cash flow functionality of the model explored the valuation capability of this tool by introducing the product's potential market revenue and captured the ramifications of delay from an NPV prospective.

CHAPTER 6

CONCLUSIONS AND FUTURE DIRECTIONS

6.1 INTRODUCTION

Declining productivity, increasing cost, and high risk of failure in pharmaceutical R&D activities create the need for effective portfolio management decision-making and implementation. Finding the optimal portfolio composition from the myriad combinations of available product candidates is further complicated by the constraints in both R&D budget and manufacturing capacity. Portfolio composition decisions separated from the explicit characterisation of the cost distributions are of little use to portfolio managers, as inadequate budget planning can cause delays that are detrimental to portfolio value realization. This chapter summarizes the efforts made in this thesis in developing computational decision tools that produce quality portfolio management solutions while providing critical cost evaluations for budget planning purpose. Future developments that advance the understanding of these subjects are also discussed.

6.2 OVERALL CONCLUSIONS

The main focus of this thesis has been the design and implementation of computational decision tools that perform fast cost evaluation of drug development process and facilitate biopharmaceutical portfolio management decision-making under uncertainty and with resource constraints. To achieve this, an activity-based, object-oriented drug development lifecycle cost model was proposed to represent the biopharmaceutical portfolio development activities of both clinical and non-clinical aspects. This tool was implemented in Chapter 3 to benchmark the cost of developing and manufacturing therapeutic biologics across the drug development lifecycle. The costs, durations, risks and interdependencies of clinical trial, manufacturing, and process development activities were captured on a single product and portfolio development basis. Three representative clinical risk profiles and two industrially relevant average stage cost

alternatives were utilised in formulating case studies that lead to the analyses of clinical and non-clinical costs required at each phase of development to ensure a market success each year. The costs of process development and manufacturing activities at each stage and their proportion of the total cost were also investigated under these risk profiles and cost scenarios. Link between the efforts that minimize the risk of delay and their economic implications in cost evaluation was established through a probabilistic approach that applied uncertainties to the durations of activities.

The drug development lifecycle cost model was also implemented to benchmark the cost of developing cell therapy product portfolio aiming at one market success. In Chapter 5, the differences between cell therapy product and biopharmaceutical drugs in manufacturing process and clinical trial size were discussed and the out-of-pocket cost for developing a single cell therapy product was estimated. The cost evaluations of portfolio development for biopharmaceuticals and for cell therapy products aiming at one market success were compared, highlighting the cost characteristics that involve non-clinical activities and their propositions to the total portfolio development cost. The possibility of inaccurate estimate of clinical success rates was addressed by exploring the impact of changing Phase II transition probability on the evaluation results. The analysis of delay was further extended in this chapter by capturing its potential damage to portfolio NPV.

The biopharmaceutical portfolio management stochastic optimization tool was designed based on the drug development cost model that functions as the evaluation engine with Monte Carlo simulation techniques to capture the drug development uncertainties and dynamic simulation mechanisms to resolve resource allocation. Performance assessments to biopharmaceutical portfolio management solutions were produced by this evaluation engine in the form of NPV distributions. A binary string representation of portfolio management decisions was introduced for its flexibility, efficiency, and simplicity. The two key statistics of NPV distributions, the average positive NPV and the probability of NPV being positive, were utilised as the

measurements of portfolio profitability and risk. A multi-objective evolutionary algorithm was implemented to efficiently search the decision space for optimal solutions. Data management system that produces data reports of various formats was designed to capture the performance of the optimal solutions as well as details in simulation at activity level.

This tool was implemented in Chapter 4 for optimization of biopharmaceutical portfolio management decision-making under effective budget and capacity constraints. A hypothetical product candidate pool was formulated with products of distinct risk-reward characteristics. This candidate pool was further diversified in a case study by varying the starting stage for R&D and factoring in upfront payment. The tool was applied to both scenarios, and the sets of optimal solutions as well as their cost distributions across development timeline and activity categories were discussed. The impacts of changing budget and capacity constraints were investigated from both decision-making and implementation perspective. Finally, the tool was utilized to explore critical transition boundaries that distinguish an in-licensing deal from "absolute value gain" to "inefficient transaction" in a portfolio context.

In conclusion, this work contributes to the effort of providing quantitative support to portfolio management decision-making in biopharmaceutical industry. The benefit of combining cost evaluation with portfolio optimization was illustrated through the enhanced understanding of drug development process, which would lead to better performance in implementing portfolio management solutions. The tools developed in this thesis is flexible for adjustment with changing landscape of industrial pipeline development, and can be altered to accommodate decision-makers with various resource attributes. Effective use of the optimization and cost evaluation outcomes can provide more specific guidance to drug development process from portfolio management and resource allocation perspective, thus improving the financial situation of the firm and creating value for society.

6.3 FUTURE WORK

The tools developed in this thesis contribute to the effort of providing the portfolio management decision makers with quantitative support. Several improvements can be made by integrating some key techniques.

Firstly, more advanced multi-objective evolutionary algorithms can be applied to enhance the performance of the optimization process. Researches on meta-heuristics have provided algorithms that suit different problems. Comparisons of performances between different search algorithms can be made from efficiency and robustness perspectives to identify better solutions. A worthy alternative to NSGA-II would be the recently developed indicator-based evolutionary algorithm (IBEA).

Secondly, as the risk indicator, the possibility of NPV being positive does not scale when the distribution of NPV has larger variations from zero. A tenth of a million dollar NPV cannot be reasonably regarded as "positive" when the maximum NPV is a hundred million. A more intelligent risk indicator can be developed so that it reflects the magnitude of NPV variations by re-defining what is an effective "positive".

Thirdly, the data generated in running of the tools can be more effectively managed through relational databases. The existing data management system designed for the tools can benefit from database normalization operations provided by relational database, as the data collection processes are mostly accomplished by multi-dimensional arrays. Using relational databases also enables remote access to data and encourages collaboration.

Finally, the simulation model can be made more dynamic after variable cost-of-capital is introduced. The firm's cost-of-capital is dependent on its capital structure, which is in turn dependent on financing activities resulted from increasing R&D budget.

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