Production Planning of Biopharmaceutical Manufacture

by

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Abstract

Multiproduct manufacturing facilities running on a campaign basis are increasingly becoming the norm for biopharmaceuticals, owing to high risks of clinical failure, regulatory pressures and the increasing number of therapeutics in clinical evaluation. The need for such flexible plants and cost-effective manufacture pose significant challenges for planning and scheduling, which are compounded by long production lead times, intermediate product stability issues and the high cost – low volume nature of biopharmaceutical manufacture. Scheduling and planning decisions are often made in the presence of variable product titres, campaign durations, contamination rates and product demands. Hence this thesis applies mathematical programming techniques to the planning of biopharmaceutical manufacture in order to identify more optimal production plans under different manufacturing scenarios. A deterministic mixed integer linear programming (MILP) medium term planning model which explicitly accounts for upstream and downstream processing is presented. A multiscenario MILP model for the medium term planning of biopharmaceutical manufacture under uncertainty is presented and solved using an iterative solution procedure. An alternative stochastic formulation for the medium term planning of biomanufacture under uncertainty based on the principles of chance constrained programming is also presented. To help manage the risks of long term capacity planning in the biopharmaceutical industry, a goal programming extension is presented which accounts for multiple objectives including cost, risk and customer service level satisfaction. The model is applied to long term capacity analysis of a mix of contractors and owned biopharmaceutical manufacturing facilities. In the final sections of this thesis an example of a commercial application of this work is presented, followed by a discussion on related validation issues in the biopharmaceutical industry.

The work in this thesis highlighted the benefits of applying mathematical programming techniques for production planning of biopharmaceutical manufacturing facilities, so as to enhance the biopharmaceutical industry's strategic and operational decision-making towards achieving more cost-effective manufacture.

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Chapter 1

Introduction

1.1. Biopharmaceutical Development

The discovery of recombinant DNA and monoclonal antibody technologies in the 1970s marked the birth of the biopharmaceutical industry. Biopharmaceuticals include protein hormones, engineered protein-based vaccines, and monoclonal antibodies. They have proven highly successful in modifying patient physiology often with greater success and fewer side effects than traditional small-molecule drugs or vaccines; in fact Walsh reports that since 2000, over a quarter of all new drugs approved have been biopharmaceuticals (Walsh, 2003). However they are fast becoming victims of their own success. As the industry matures companies continue to face a long and costly product development lifecycle, with an average time-to-market of 7-8 years (Foo et al. 2001), high risks of clinical failure, regulatory pressures and the inherent complexities of biopharmaceutical manufacture all present real challenges for companies wishing to remain competitive by achieving more cost-effective biomanufacturing. This need to reduce costs and make better use of resources provides the impetus for the development of decision support tools (DST) for the biopharmaceutical industry and the motivation for this EngD.

1.2. Biopharmaceutical Manufacture

Biopharmaceutical manufacture or "biomanufacturing" refers to the process of producing a biologic or biopharmaceutical, and is generally taken to be the process which ensues subsequent to the stages of research and process development (Sofer & Hagel, 1997). A typical biomanufacturing process is likely to be comprised of a number of steps, typically cell culture/fermentation, cell harvesting, recovery, purification and formulation through to a product with regulatory approval. Each step comprises a number of unit operations, surrounded by a number of ancillary but vital processes such as cleaning, sterilisation, media/buffer preparation and quality control and quality assurance steps.

Bioprocessing is characterised by a number of manufacturing challenges shared with the traditional chemical batch processing industries, where typically the major operational challenges are the need to speed up process/product development, increase productivity, and satisfy safety and product quality requirements (Allgor *et al.*, 1996). However there are additional challenges in the biopharmaceutical industry, such as higher variations in process behaviour due to the biological nature of the materials used, more stringent quality control regulations and higher end-product purity requirements (due to the sensitive therapeutic nature of many of the products). Other challenges in bioprocessing include the ongoing improvement of fermentation titres and downstream purification yields, management of utilities which are often shared between different process equipment and a general need for ongoing process optimisation.

Much of biopharmaceutical production has traditionally been undertaken in dedicated facilities due to the stringent regulatory constraints associated with biopharmaceutical manufacture which stems from the need to avoid product cross-contamination. However, in the 1990's this started to change as smaller companies, unable to cope with the capital outlay associated with building their own facilities, were driven to use the services of contract manufacturers (Sofer, 1995). This gave rise to the now widespread use of multiuse, multiproduct facilities. The trend was accelerated in 1998 when the Food and Drug Administration (FDA) started to allow companies to manufacture different products in the same building, with some shared

facilities, since this was found to result in increased efficiency and facility utilisation (Chemical Market Reporter, 1998). The high risks associated with drug development coupled with increasing demands for certain therapeutics has meant that an increased use of the more flexible and cost-effective multiproduct contract manufacturing facilities, and in 2004 Langer reported that 35% of all biomanufacturers outsourced at least some of their production, expecting that by 2008 nearly half would do this (Langer, 2004). Given the flexibility offered by multiproduct facilities, contract manufacturers are not alone as the majority of biomanufacturing companies are employing multiproduct facilities. Multiproduct facilities pose a significant cleaning validation challenge. Products are typically run one at a time on a campaign basis, this poses a serious risk of cross-contamination if the necessary precautions are not taken or detection methods are not sufficiently sensitive and validated. Furthermore, equipment may be disposable, dedicated or shared. Each presents different advantages and disadvantages, in terms of cost effectiveness and risks of contamination, and frequency of maintenance and cleaning. At a higher level, biomanufacturers need to think about capacity availability for products which may or may not be successful. Challenges are particularly great in larger companies which may have a very large portfolio of drugs going through their development pipeline at any one point in addition to their existing marketed drugs. Manufacturers have to decide whether to build or buy capacity, which is a particularly sensitive financial decision given the associated costs and risks such as potential loss of market.

1.3. Planning and Scheduling of Biopharmaceutical Manufacture

As was discussed in Section 1.2, the biopharmaceutical industry is increasingly employing multiproduct manufacturing facilities. Challenges include the significant burden of cleaning validation and the risk of cross contamination. Other challenges include the time and cost associated with campaign changeovers due to equipment setup and cleaning. The particularly long lead times associated with changeover, coupled with sensitive and costly intermediate storage product conditions present a

significant challenge for production planning and scheduling. These are often compounded by inherent technical uncertainties that can impact costs and delivery. These include fluctuations in fermentation titres, purification yields, campaign lengths, product demands and contamination rates (Farid *et al.*, 2005). Gosling (2003) notes that significant economic benefits can be expected if these planning and scheduling challenges can be overcome. Better scheduling and planning is likely to improve plant capacity utilisation and thereby lead to increased productivity. In fact recent industrial reports (Fox, 2005) confirm that improved plant utilisation leads to increased sales and profitability.

An increasing number of large-scale biopharmaceutical companies have a portfolio of commercial products on the market as well as a pipeline of candidates under clinical evaluation. Developing a comprehensive manufacturing strategy to meet anticipated demands for both clinical trial and market material requires careful capacity planning. The launch of successful commercial products has often triggered companies to bridge in-house capacity via strategic partnerships with contract manufacturing organisations (Gottschalk 2005, Kamarck 2006). Consequently, more effective methods are required to manage and align production across several multiproduct facilities, including third party organisations, so as to ensure the availability of sufficient capacity. However, determining capacity needs for biopharmaceutical production is often a difficult process requiring predictions of product doses, market forecasts, production rates (titres, yields) and clinical/technical success rates. The issue of planning and scheduling is a major component within the key business and strategic issue of long term capacity management which remains at the forefront of the minds of the biopharmaceutical industry's decision-makers since Immunex's capacity shortage for the manufacture of its highly successful drug Enbrel and the resulting financial losses (Thiel, 2004).

1.4. Modelling Biopharmaceutical Manufacture

Many benefits are to be reaped through the implementation of computer modelling (as will be discussed in Section 1.5), however the effectiveness of computer

modelling is often limited by the complexity of the process which is to be modelled. Saraph (2001) notes some of the key features of biomanufacturing from a modelling perspective:

- A typical biomanufacturing process is a mix of discrete and continuous processes.
- The batch sizes vary from stage to stage.
- Different production stages are physically and temporally separated by intermediate quality control and quality assurance processes.
- Storage capacities at each stage differ.
- Product has limited shelf life at each stage of production and product potency is adversely affected by storage.
- Production capacity differs from stage to stage and so does staffing.
- There is no re-entrant flow of material.
- There are elaborate controls to ensure required cleanliness, which create further operational constraints.
- Sharing of common utilities.

Mustafa *et al.* (2006) note the scarcity of trained personnel and limited availability of fundamental physical property data as being some of the factors attributing to a lack of modelling work in the biopharmaceutical industry as compared to more established industries such as the chemical industry.

1.5. Objectives of Decision Support Tools

A decision support tool or system (DST) is defined broadly by Finlay (1994) as "a computer-based system that aids the process of decision making". Computer based tools which meet this definition are used extensively within the biopharmaceutical industry for a vast number of purposes ranging from accounting, lab-management, process development, risk-management, cost-benefit analysis, process scheduling

and ongoing process optimisation. However in this thesis the focus is on those used to aid manufacturing decisions.

Saraph (2001) proposed some relatively generic objectives for a DST that was used to aid biomanufacturing decision-making:

- To develop a better understanding of the existing manufacturing operations and capability.
- To identify the root causes, and potential solutions of operational problems.
- To analyse proposed solutions.
- To help in forecasting in order to identify potential opportunities and avoid potential pitfalls.
- To support the strategic decision making process which may consider a variety of features whether process, logistical or financial.

Williams (1999) proposed some typical objectives more specific to mathematical model building:

- To gain insight into the problem. The actual exercise of building a mathematical model often reveals relationships that were not apparent previously. As a result greater understanding of the problem is achieved.
- To identify non-obvious solutions to the problem. Having built a model it is then possible to analyse it mathematically and help suggest a course of actions that might not otherwise be obvious.
- To investigate extreme aspects of the problem. Computational experiments can be conducted when it is not possible or desirable to conduct an experiment in real-life (e.g. accident simulation models) and provide us with useful information concerning the problem under investigation.

Between the two sets of objectives, a good idea of the value decision support tools can add within the biopharmaceutical industry can be seen.

1.6. Aims and Objectives

The aim of this work is *to facilitate the biopharmaceutical industry's strategic and operational decision-making by applying mathematical programming techniques for production planning of biopharmaceutical manufacturing facilities.* It is motivated by the need for improved cost-effectiveness and better capacity management in the biopharmaceutical industry.

In order to achieve these goals, the following areas will be addressed:

- *Medium term planning*: this area is concerned with determining the optimal medium term production plans for a multiproduct multi-suite biopharmaceutical manufacturing facility. It will do so by capturing the characteristic bioprocessing features of the production planning problem in the biopharmaceutical industry.
- *Medium term planning under uncertainty*: this area is focused on understanding the impact of uncertainty on biopharmaceutical manufacturing production plans and the development of alternative approaches for the determination of the optimal medium term production plans for a multiproduct biopharmaceutical manufacturing facility under uncertain manufacturing conditions. Solutions should be achieved within a reasonable computational time without compromising the quality of the obtained solution.
- *Long term planning*: this area deals with longer term capacity management of biopharmaceutical facilities and the need to understand better existing capacity capabilities and to quantify the impact of different strategic operating polices on capacity decisions.

1.7. Thesis Outline

The thesis is structured as follows:

Chapter 2 presents a critical review of past work on production planning within the biopharmaceutical and associated industries, considering deterministic planning

works in the medium and long term timescales, followed by a review of planning under uncertainty.

In Chapter 3, a deterministic mathematical programming formulation for medium term planning of biopharmaceutical manufacture is presented. The model is applied to two illustrative examples and is compared with an industrial rule-based approach.

Chapter 4 proposes a stochastic mathematical programming formulation based on two-stage programming for the medium term planning of biopharmaceutical manufacture under uncertainty. A hierarchical algorithm for the efficient solution of the problem is also presented and compared with the full space problem and a rolling horizon algorithm via a number of illustrative examples.

An alternative stochastic mathematical programming formulation based on chance constrained programming for the medium term planning of biopharmaceutical manufacture under uncertainty is presented in Chapter 5. The deterministic equivalent formulation is derived and compared to the approach presented in the previous chapter.

A multiobjective optimisation framework based on goal programming is proposed and used to tackle the problem of long term planning in the biopharmaceutical industry in Chapter 6. The problem is applied to an industrial case study and insights are drawn through a variety of studies.

Chapter 7 presents a plan for the commercialisation of this work and Chapter 8 discusses the related validation and regulatory issues.

Finally, Chapter 9 concludes the thesis summarising the work that has been done and outlines possible directions for future work in the area of production planning of biopharmaceutical manufacture.

Chapter 2

Literature Survey

Planning and scheduling is a vital component of cost-effective manufacturing operations in the biopharmaceutical and process industries in general. Planning and scheduling activities are very closely related, as the decisions made at the planning level have a strong influence on scheduling. Hence, it is necessary to make a distinction between the two activities as the focus of this work is that of production planning rather than scheduling. Usually, planning means the generation of production plans for longer periods of time typically months to years, given forecasts for prices and product demands. In contrast, scheduling refers to the assignment of resources to activities, sequencing of activities and determination of starting and ending times for the execution over a short period of time, typically days to weeks.

In this chapter the key works of relevance to the problem of production planning of biopharmaceutical manufacture are reviewed. First the general problem of planning and scheduling in the biopharmaceutical industry is discussed highlighting some of the related works in this area (Section 2.1). Deterministic planning works in the closely related process industries are then presented (Section 2.2), this is followed by works in the area of planning under uncertainty (Section 2.3). Finally, concluding remarks are drawn whereby the scope and the motivation of this work are clarified in the light of earlier work (Section 2.4).

2.1. Planning and Scheduling in the Biopharmaceutical Industry

Planning and scheduling of biochemical processes has received relatively little attention. To date, custom planning methods used by biomanufacturers remain relatively simplistic e.g. spreadsheets and t-cards using industrial experience/common sense approaches, typically supported by enterprise and material requirement planning (ERP & MRP) software which are often limited to customer order, inventory and resource management. To some extent this can be attributed to the lack of relevantly trained personnel (Mustafa *et al.*, 2006). However, given the potentially vast number of possible solutions due to the combinatorial nature (exponential growth in solution space with linear growth in problem size) of scheduling and planning problems, it is clear that there is significant scope for improvement. General and specialist bioprocess simulation software packages have been used for solving planning and scheduling problems within the biopharmaceutical industry.The packages have mostly been used for debottlenecking of equipment and utility usage, examples include Batch Plus (Shanklin *et al.*, 2001), Chemsim (Gosling, 2003) and SuperPro designer (Petrides and Siletti, 2004). However industrial accounts highlight their inadequacy when challenged with dealing with larger problems involving multiple products and suites. These packages probably remain best suited to "what if" scenario-based analysis, whereby manufacturing challenges such as the impact of resource bottlenecks and delays on schedules are evaluated through discrete event simulation techniques.

Most recent published optimisation/mathematical programming approaches for planning and scheduling of biochemical processes have focused on the short term time scale. Examples of such approaches include the work of Iribarren *et al.* (2004), where an approach for simultaneous process development and short term process scheduling for recombinant protein production is developed. Samsatli and Shah (1996) devised a scheduling approach for short term batch process scheduling of biochemical processes based on the State Task Network (STN) formulation proposed by Kondili *et al.* (1993). Most recently Tsang *et al.* (2006) presented a planning and

scheduling model applied to a flu vaccine manufacturing facility whereby planning for upstream/downstream production was tackled via a heuristic scheduler and detailed scheduling via an optimisation model based on the STN formulation. The applicability of the model was demonstrated via a number of debottlenecking studies on cleaning operation and installation of new equipment items. Industrial accounts also indicate that more recently mathematical programming based systems are being considered for deployment in the industry, especially for larger scale planning and supply chain problems.

2.2. Production Planning: Deterministic Optimisation Models

The bulk of relevant research in the area of production planning has been conducted on and applied to the traditional batch process industries. Of particular relevance and similarity are the pharmaceutical, food and beverage and speciality chemicals industries, which share some of the key features of the biopharmaceutical production planning problem. The main similarity between these industries is the use of a batch mode of operation to produce often small quantities of a large number products using multipurpose equipment. Batch production involves an integer number of batches where a batch is the smallest quantity produced, with batches often produced in long sequences, referred to as a "campaign", to avoid changeover delays, contamination risks and cleaning costs.

Kallrath (2002) notes some of the key structural objects in planning models used in the process industries which are also shared with the biopharmaceutical industry:

- *Locations* are often used for production and storage sites.
- *Facilities* are often characterised by functional properties such as capacity, throughput rates, product recipes, yields, fixed and variable costs or storage limitations.
- *Demand points* are used to represent customers, regional warehouses or distributors who specify the amount of product they request.

- *Inventories* may be tanks or warehouses which can be fixed or movable entities, with product storage being either product specific or global.
- *Products* may be classified as raw materials, intermediates or finished and salable products, where product demands may be characterised by volume, selling price, package type, time, origin and/or location.
- *Suppliers* which may provide product under different offering schemes.

Models used for planning in the process industries may involve a very large variety of manufacturing and logistical features. Some of the key features shared with the biopharmaceutical manufacturing planning problem are detailed below:

- *Batch production* enforcing the production of an integer number of batches at a predefined batch size.
- *Buying, building, closing or selling* manufacturing sites.
- *Campaign production* enforcing the production of a minimum number batches in sequence.
- *Penalty costs* applied if deliveries arrive after their due dates.
- *Multiple locations* can be used for production sites, storage sites or demand points.
- *Multi-stage production* allowing for the production of multiple intermediates and their intermediate storage before the manufacture of the final product.
- *Multiple time periods* for definition of the time horizon which can be *continuous* with non equidistant time periods or *discrete* fixed size time periods.
- *Product Shelf-life* allowing for product aging to be traced and *product disposal* for expired products.

Planning is part of the supply chain management problem and typically focuses on medium term sales and inventory planning or more long term strategic planning and capacity analysis. Hence we divide the review of the key works into two parts, medium term planning and long term planning.

2.2.1. Medium Term Planning

The medium term planning timescale typically refers to a duration of a few months up to a few years and is also often referred to as production scheduling, campaign planning or medium term planning. The research in this area is often hard to distinguish as planning or scheduling as many works attempt to address both simultaneously or address a hybrid problem composed of features from both problems.

The production planning problem in the process industries has received great attention over the years with one of the earliest noted works being that of Mauderli and Rippin (1979), but has since come a long way as practitioners have continually adapted to the industry changes and trends. Some excellent reviews of recent work have been conducted by Applequist *et al.* (1997), Shah (1998), and Kallrath (2002). Many approaches have been used for planning in the process industries, and are often divided into heuristic and mathematical programming approaches.

Heuristic methods are concerned with formulating rules for the determination of sequences of activities and include dispatching rules or rule-based approaches. They are often derived from industrial rules of thumb and used in combination with other methods to reduce the resulting problem size and complexity when solving real-life problems, often at the cost of achieving sub-optimal solutions. Dispatching rules are more commonly associated with scheduling problems; however, they have also been applied to planning problems. Some relevant dispatching rules are: First come first served (FCFS), Earliest due date (EDD), Shortest processing time (SPT), Longest processing time (LPT), Earliest release date (ERD) and Weighted shortest processing time (WSPT). Pinedo (2002) details some useful dispatching rules commonly used in scheduling practice.

Meta-heuristic or Stochastic-search methods are products of the evolution of heuristic-based approaches and typically involve the simulation of a given system and the evaluation of its objective function. They have been used to tackle planning problems in the process industries; examples include Genetic Algorithms, Simulated Annealing and Tabu Search. These methods have in common that they lack proof of convergence and a dependable measure of solution quality. However, they can often

be effectively used to improve a given solution by performing a local search and achieve sub-optimal solutions within reasonable time-scales where more rigorous mathematical programming based methods may fail. Examples of Metaheuristic methods are detailed below.

Genetic algorithms (GA) (Goldberg, 1989) are Metaheuristic methods that use techniques inspired by evolutionary biology such as inheritance, mutation, selection, and crossover. GA's are typically implemented as a computer simulation in which a population of abstract representations (called chromosomes) of candidate solutions (called individuals) to an optimisation problem evolves toward better solutions. Löhl *et al.* (1998) compared a GA and a mathematical programming approach for sequencing and scheduling of a polymer production process and found the GA to be a better approach if an improved solution was needed quickly. However, it generally underperformed in terms of solution quality when compared with the mathematical programming approach. More recently, Berning *et al.* (2004) presented a Genetic algorithm for planning and scheduling within a general framework for integrated supply chain management in the chemical process industry. Their algorithm considered the production schedules of all the plants involved simultaneously and provided a better overall solution than one obtained by individually optimising production schedules.

Simulated annealing (SA) (Kirkpatrick *et al.*, 1983) links the probability of accepting a solution which is worse than the reference solution to a temperature-like parameter based on an analogy which describes the cooling of metals. One of the earliest applications to planning and scheduling was by Ku and Karimi (1991) in which it was applied to the scheduling problem of chemical batch processes. Tandon *et al.* (1995) presented an SA algorithm for minimising tardiness (difference between completion time of late products and their prior due dates) in a network of single stage, unrelated parallel units. The algorithm was found to outperform an established heuristic improvement method in larger test problems. Lee and Malone (2000) proposed an SA algorithm for batch process planning of a multi-plant structure and compared the approach with a number of dispatching rules, whereby the SA algorithm was found to be superior in terms of solution quality. Ryu *et al.* (2001) presented an SA algorithm for production scheduling based on the minimisation or

earliness and tardiness when meeting due dates. They demonstrate the approach to find good solutions in relatively short computational times.

Tabu search (TS) (Glover and Laguna, 1997) is essentially an adaptive local neighbourhood search procedure. It hierarchically directs one or more local search procedures in an aggressive pursuit of the global optimum, while using memory functions to avoid being trapped in local optima. The work of Barnes and Laguna (1993) was one of the first successful applications of TS to production scheduling. Oh and Karimi (2001) developed a TS implementation for the solution of a mixed integer non linear programming (MINLP) formulation applied to campaign sequencing and scheduling of an industrial sized problem. A more recent application is that of Bhushan and Karimi (2004) in which TS and SA algorithms were developed for the solution of a continuous-time mixed integer linear programming (MILP) formulation for scheduling production an automated wet-etch station. The TS algorithm was found to outperform the SA algorithm, achieving near optimal solutions.

Shah (1998) notes that although heuristic approaches are more representative of current industrial practice, the bulk of planning and scheduling research has been more directed towards the development of mathematical programming approaches as they are able to represent the majority of the interactions present. Some of the general benefits of mathematical programming were discussed in Section 1.5. More specifically mathematical programming problems with a convex solution structure are able to provide a proof of convergence and a dependable measure of solution quality. For these reasons planning and scheduling problems are most commonly formulated as mixed integer linear programming (MILP) problems in which an objective function is maximised or minimised subject to constraints. The most common planning applications in the batch process industries include campaign planning and sequencing models in which the optimal quantities and sequence of manufacturing campaigns is determined, and aggregate planning and scheduling approaches in which a rough cut production plan is determined which forms the basis of input data for detailed short term scheduling.

Papageorgiou and Pantelides (1996a) presented a comprehensive review of earlier work on campaign planning and proposed a general formulation for the problem. In a companion paper (Papageorgiou and Pantelides, 1996b), where computational issues were discussed, a decomposition approach for the efficient solution of larger/practical problem instances was presented. McDonald and Karimi (1997) presented a medium term planning model for parallel semicontinuous processors (multiple facilities or production lines) where they incorporated minimum-campaign-length constraints in their formulation, but did not consider the detailed timings of campaigns. Karimi and McDonald (1997) also presented two multiperiod, continuous-time formulations for the detailed timings of campaigns using time slots in a companion paper. Ierapetritou and Floudas (1998a) introduced a continuous time formulation for production scheduling of batch processes, which was later extended and applied to continuous and semicontinuous processes (Ierapetritou and Floudas, 1998b). In the previous two formulations demands were due at the end of the time horizon; the authors later extended the work to allow for multiple intermediate due dates (Ierapetritou and Floudas, 1999), and found their proposed approaches to perform favourably in each case when compared to similar work in the literature. Gupta and Maranas (1999) developed a hierarchical Lagrangean relaxation procedure for the solution of the earlier medium term planning model by McDonald and Karimi (1997). When applied to tackling large-scale problems the approach was found to make considerable computational savings as compared to direct solution via commercial MILP solvers. Oh and Karimi (2001a) presented an MILP model for production planning assuming a single production line and sequence dependent set-up times for in optimal lot (batch) sizing. An equivalent MILP formulation was derived and solved using three different problem specific heuristic-based algorithms. Oh and Karimi (2001b) later developed an MINLP formulation for the sequencing and scheduling of the lot sizing problem with a Tabu search implementation for its solution. Whereas the previous models of Oh and Karimi (2001a, 2001b) were based on a single production line assumption, Lamba and Karimi (2002a) presented an MILP model for scheduling multiproduct facilities with multiple production lines. They later introduced (Lamba and Karimi, 2002b) a two-step decomposition scheme in which the problem was decomposed into campaign generation, and campaign

sequencing and scheduling. Lim and Karimi (2003) used asynchronous time slots and showed improvements on the work by Lamba and Karimi (2002a, 200b) which assumed synchronous timeslots (such that the total resource usage or the total production at any time within a period can be seen). Jackson and Grossman (2003) proposed a multiperiod nonlinear programming model for the production planning and product distribution of several continuous multiproduct plants located at different sites and supplying different markets. They developed spatial (between plants and markets) and temporal (between time periods) solution techniques based on Lagrangean decomposition for the problem's efficient solution.

In many planning formulations reported in the literature a discrete representation of time is used; however this often presents difficulties when a very large number of time periods are required for the modelling of the necessary time granularity. Hence, a number of authors have presented temporal aggregation methods in which larger time-slots are used at the planning level and more detailed time-periods are used for short term scheduling decisions. Wilkinson *et al.* (1995) were one of the first to apply such approaches in the process industries. They applied a general temporal aggregation scheme for planning and scheduling to the RTN (resource task network) scheduling formulation approach presented by Pantelides (1994), later applying their time aggregation /disaggregation approach to a three-plant and 100 product supply network problem based on an industrial case-study (Wilkinson *et al.*, 1996). Basset *et al.* (1996a, 1996b) presented an aggregation procedure based on a similar temporal aggregation concept similar to that of Wilkinson *et al.* (1995, 1996) for the aggregation of large-scale problems using the STN formulation. Both authors implemented a backward rolling horizon algorithm, however Basset *et al.* (1996a, 1996b) also aggregated tasks and units. Dimitriadis *et al.* (1997) proposed a similar aggregation approach based on the RTN formulation; however their concept was based on fixing binary variables in the MILP model for the time window under consideration. A more recent application of aggregation techniques in the pharmaceutical industry is that of Grunow *et al.* (2003), where they employ a number of different aggregations, specifically aggregating processing tasks into cascades, equipment units into sub-plants, and individual material-flows into material-flow patterns, while also employing a demand disaggregation procedure.

2.2.2. Long Term Planning

Long term planning is concerned with strategic planning decisions often taken in years ahead of time. The most commonly tackled long term planning problem is that of capacity planning and product portfolio management (although the focus here is on the former), and is typically concerned with the best use of limited resources in the strategic decision-making related to new product development, the associated investments decisions for new manufacturing capacity and the necessary planning of production runs. This problem is of particular relevance in the pharmaceutical and biopharmaceutical industries where new products represent the lifeblood of the industry. A recent review of the pharmaceutical supply chain problem which covers relevant capacity planning work in the pharmaceutical industry is presented by Shah (2004). Shah (2005) later presents a review of process industry supply chains where more general work on capacity planning in the process industries is covered.

One of the earlier works presented in the process industry literature is that of Sahinidis *et al.* (1989) where they presented a multi-period model for the optimal process selection from a network of competing processes, the determination of the timing and sizing of any necessary process expansions and the optimal production amounts. Liu and Sahindis (1996a) presented a tighter linear programming (LP) relaxation of the earlier model by Sahinidis *et al.* (1989) and used a cutting plane approach for the efficient solution of a problem involving a large network of chemical processes. Jain and Grossmann (1999) presented two different MILP formulations for the resource constrained scheduling of testing for new product development. Papageorgiou *et al.* (2001) considered the capacity planning problem in the pharmaceutical industry where new manufacturing capacity could be allocated to existing or new sites. The focus of the work was that of modelling financial flows and taxation issues pertinent to global trading. Most recently Sundaramoorthy and Karimi (2004) presented a multi-period, continuous-time, MILP model that addresses the campaign planning problem in pharmaceutical production and considered strategic decisions surrounding the potential outsourcing of production tasks, they illustrated the effects of new product introductions on plant production plans, the

benefits of outsourcing, and sudden plant/demand changes through a number of illustrative examples.

Given the considerable uncertainty associated with long term decisions many relevant capacity planning works in the literature allow for the impact of uncertainty in making strategic decisions. Hence the remaining works on long term planning will be covered in the following section where relevant work considering the representation and solution of problems involving uncertain parameters and related issues will be reviewed.

2.3. Production Planning under Uncertainty

The applications discussed thus far clearly illustrate the utility of optimisation models in improving productivity and profitability in manufacturing operations. However, the presence of various uncertainties in the process industries (e.g. uncertainty in production rates and costs, demand, raw material availability, prices etc.) complicates the optimisation process. This is particularly true of planning and scheduling problems where plans or schedules that do not account for uncertainty may be rendered unsatisfactory in quality or even infeasible. Hence, in cases where uncertainty is found to have a considerable impact on performance, planning approaches should incorporate the relevant uncertainties in their proposed modelling assumptions. In the next sub-section relevant works in the bioprocess literature are highlighted, and in the following sections the application of general approaches for optimisation under uncertainty to production planning in the process industries are reviewed and discussed.

2.3.1. Uncertainty in the Biopharmaceutical Manufacture

The planning and scheduling of biopharmaceutical manufacture is complicated by inherent technical uncertainties that can impact costs and delivery. These include fluctuations in fermentation titres, purification yields, campaign lengths, product demands and contamination rates (Farid *et al.*, 2005). Many of these fluctuations directly impact the core decisions taken in planning and scheduling. For example,

variable fermentation titres (grams of product per litre of broth) directly determine the number of batches required to satisfy product demands and hence impact on customer demand satisfaction and profitability.

Recently, discrete event simulation techniques have gained popularity for modelling the logistics of operations and studying the impact of bioprocess uncertainties. Recent work includes simulation studies which look at the impact of various uncertain parameters on both operational and financial outputs. Most recently, Brastow and Rice (2003) used simulation modelling to help answer a variety of strategic questions associated with the drug development lifecycle, they considered a number of different case studies based around analysing different manufacturing capacity strategies and quantifying the impact of uncertainty via Monte-Carlo simulation. Farid *et al.* (2005) used Monte-Carlo simulation to consider the impact of uncertainty in product titres, demands and market penetration on different manufacturing strategies for the production of biopharmaceutical drug candidates. Lim *et al.* (2005) used a similar technique to consider the impact of uncertainty in product titres, downstream processing yield and contamination rates on different pooling strategies for perfusion culture type processes, while Biwer *et al.* (2005) investigated the impact of uncertainty in various technical, supply chain and market related parameters on penicillin V production. The work of Rajapakse *et al.* (2005) employed Monte-Carlo simulation to study the impact of key technical and market uncertainties on the biopharmaceutical drug portfolio problem and highlighted the benefits of incorporating uncertainties when ranking different manufacturing and capacity planning strategies. The aforementioned works share the focus of improving decision making given the key sources of uncertainty within the commercial biomanufacturing environment and demonstrate that the modelling of key uncertainties can aid risk mitigation and result in more effective use of resources and improved overall economic performance.

2.3.2. Optimisation under Uncertainty

For simplicity in modelling large-scale optimisation problems, variability can in some cases be ignored and modellers can assume that the parameters of the problem are exactly known or that they can be approximated (or forecasted) with a very small

margin of error. This is done because it results in a model that is easier to solve. However, in most cases these parameters have an underlying probability distribution and should be modelled as random variables. This clearly complicates the problem but, on the other hand, makes the results obtained more realistic. There are a number of different ways of incorporating this randomness into the overall model.

Traditionally, the treatment of uncertainty is realised through the use of stochastic optimisation approaches. These approaches recognise the presence of multiple data instances that might be potentially realised in the future. The optimisation models then attempt to generate a decision that maximises (or minimises) an expected performance measure, where the expectation is taken over an assumed probability distribution. In many cases, when multiple uncertain factors exist in the input data, assumptions of distributional independence among factors are made. After possible scenarios (data instances) or probability distributions are fed into a model, a stochastically optimal solution is generated. Sahinidis (2004) presented a recent review of the literature on optimisation under uncertainty. The topics covered include two-stage programming, probabilistic (chance) programming, fuzzy programming and dynamic programming. Biegler and Grossmann (2004) presented a general review of past optimisation work where the key advances in optimisation under uncertainty were covered.

Most optimisation under uncertainty problems are typically represented via *two-stage* or *multistage* (more than two stages) stochastic programming formulations (We refer the reader to Kall and Wallace (1994) and Birge and Louveaux (1997) as basic references for the theory and application of two-stage stochastic programs). In two-stage programming strategic decisions are made in a first stage (here and now) while operational decisions are made in a second stage (wait and see) through the introduction of future "scenarios" for different realisations of uncertain events. The characteristic challenge of such problems is the inevitable explosion in the number of scenarios with increasing products and/or outcomes. Hence, multi-stage programming problems typically require solution via efficient solution procedures such as scenario aggregation (whereby certain scenarios are strategically identified and aggregated) and problem decomposition procedures (for example the breakdown of the overall problem into smaller sub-problems where decisions are fixed, and then

later solving a larger problem with binary variables fixed) which exploit the specific problem's structure (Kall and Wallace, 1994). The resulting explosion in problem size often leads to large-scale combinatorial optimisation problems which can be also be solved though the use of heuristic algorithms which have been discussed above in Section 3.2.1. Reeves (1995) presents a number of modern heuristic techniques for large-scale combinatorial problems (simulated annealing, Tabu search, Genetic algorithms, Lagrangean relaxation and decomposition), while Wolsey (1998) discusses several heuristic algorithms for the solution of integer programming problems (dive-and-fix, relax-and-fix, cut-and-fix).

There have been many applications of two-stage and multistage-programming techniques to planning in the process industries in recent years. Such work includes that of Ierapetritou and Pistikopoulos (1994a) who present two-stage programming models for short term production planning and, long range planning and capacity expansion. They present a decomposition-based solution approach for the problems solution which was later extended by Ahmed *et al.* (2000) by introducing remedial measures for the avoidance of local minima. Ierapetritou *et al.* (1994b) also investigated the effect of uncertainty on future plant operation and expansion using two-stage stochastic programming formulations, they also investigated the behavioural issues surrounding the here-and-now and the wait-and-see models through the concept of the value-of-perfect-information (VPI). This value is described as the difference between the two alternative behavioural models of actions under uncertainty. Liu and Sahinidis (1996b) presented a two-stage stochastic programming approach for process planning under uncertainty and devised a decomposition algorithm incorporating Monte-Carlo sampling for the solution of the stochastic model. They also proposed a method for the comparison of two-stage programming and fuzzy programming approaches, which was found to favour two-stage programming. Clay and Grossmann (1997) developed a methodology that considered stochastic linear programming models for production planning where coefficient costs and uncertainties were represented by finite discrete probability distribution functions. They proposed a sensitivity-based successive disaggregation algorithm for the problem's solution was based on applying mean-value approximations over partitions of the problem space, and was found to outperform a

number of Bender's decomposition variants. Rotstein *et al.* (1999) presented a two-stage stochastic programming model for the capacity planning, investment strategy and product selection decisions in the pharmaceutical industry. They proposed a hierarchical scenario tree aggregation procedure for the solution of the resulting multiscenario problem and illustrated its applicability through a case study from the pharmaceutical industry.

Other more recent works addressing these problems include the work of Gupta and Maranas (2000) who formulated a two-stage stochastic model composed of a here-and-now production model and a wait-and-see inventory and distribution model based on the deterministic production planning model of McDonald and Karimi (1997). Maravelias and Grossmann (2001) presented a multi-period MILP model for the simultaneous resource constrained scheduling and planning of batch manufacturing facilities. They also developed a heuristic algorithm for the problem's solution based on Lagrangean decomposition which provided near optimal solutions. Balasubramanian and Grossmann (2002) proposed an aggregation/disaggregation branch and bound algorithm. The problem was solved in time stages, disaggregating a given stage at each stage, while aggregating the remaining stages and replacing the remaining scenarios with the mean values of the uncertain parameters. Gupta and Maranas (2003) tackled the supply chain under demand uncertainty problem. They extended their previous work (Gupta and Maranas, 2000) to incorporate some of the key features of the supply chain decision-making process under uncertainty and demonstrated the model's applicability through a planning case study. Gatica *et al.* (2003a) presented a multi-stage programming formulation for capacity planning under uncertainty in the pharmaceutical industry. The authors later developed (Gatica *et al.*, 2003b) a scenario aggregation–disaggregation approach for the problem's solution, whereby scenarios were grouped into predetermined clusters based on mapping between products and clinical trials outcomes. Balasubramanian and Grossmann (2004) compared deterministic, two-stage and multi-stage formulations with a shrinking horizon multistage programming approximation algorithm for batch scheduling based on STN type formulations. The algorithm solved a number of two-stage problems fixing the schedule as it moved along the time horizon. Oh and Karimi (2004) presented an MILP model for deterministic capacity-expansion

planning and material sourcing in chemical supply chains, which was also extended to incorporate regulatory features (corporate tax and import duty) and, uncertain demands and import duties using a simply scenario-planning approach. The focus of the work was on the modelling of the regulatory features and rather than the uncertain parameters. Finally, Levis and Papageorgiou (2004) proposed a two-stage programming formulation for pharmaceutical capacity planning and developed a hierarchical algorithm in which the first step used an aggregated version of the model, with a reduced variable space. This problem was solved initially where first stage (strategic) decision variables were calculated. In the second step, a detailed model was solved subject to the decision variables estimated in the previous step.

Given the considerable efforts involved in finding efficient solutions to multi-scenario type representations alternative approaches to problem formulation without forgoing solution quality would be ideal. Hence many practitioners have developed alternative approaches to optimisation under uncertainty and applied them to problems involving planning under uncertainty. Some of these approaches have been considered for planning in the process industries and include Chance Constrained programming, Fuzzy programming, Dynamic programming and Real-Options-based valuation.

The *Chance constrained programming* (CCP) approach was first presented by Charnes and Cooper (1959) for representing uncertain model parameters. The approach aims to satisfy constraints with a specified probability or confidence level and by leveraging concepts from probability theory provide the optimal solution at that confidence level. Relevant works incorporating chance constraints in the area of planning include that of Petkov and Maranas (1997) who proposed a stochastic extension to the multiperiod planning and scheduling model proposed by Grossmann and Birewar (1990). Faced with uncertain single or multiple product demands with prespecified probability levels (chance constraints), they proposed deterministic equivalents to the stochastic elements and investigated different modelling features and their effect on computational performance. Gupta *et al.* (2000) developed a combined CCP and two-stage stochastic programming methodology which was utilised for capturing the trade-off between customer demand satisfaction and production costs. More recently, Wan *et al.* (2005) developed a simulation based

optimisation framework applied to supply chain management and accommodated chance constraints in order to ensure service levels were met. The aforementioned works share in common the employment of chance constraints for the specification that an objective or constraint must be met with a certain probability. The characteristic challenge associated with the majority of CCP approaches within the process industry literature, including those mentioned above, involves the derivation of the appropriate deterministic equivalents of the chance constraints and the efficient solution of the resulting optimisation problem.

Fuzzy programming (Zimmermann, 1978) is a mathematical programming approach based on the fuzzy set theory of Zadeh (1965), where uncertain parameters in a mathematical model are considered fuzzy numbers defined on a fuzzy set associated with a membership function. The objective function may be a fuzzy goal or a crisp function and similarly to the CCP approach the constraints may allow some violations. Models aim to take into account a) the decision maker's expectations of a target range of the objective value and b) soft constraints based on decision making in a fuzzy environment (Bellman and Zadeh, 1970). Some recent applications to planning include Liu and Sahinidis (1997) who presented a fuzzy programming model for process planning under uncertainty and proposed a global optimisation algorithm for its solution. Balasubramanian and Grossmann (2003) proposed a fuzzy programming formulation using interval arithmetic principles and applied it to flowshop scheduling and new product development problems. They also developed a Tabu search implementation for the solution of larger cases.

Decision-making under uncertainty is broadly considered to have two major branches, stochastic programming techniques (which have thus far been covered) and stochastic optimal control or Markov decision processes which are mathematical frameworks for modelling decision-making in situations where outcomes are partly random and partly under the control of the decision maker. More specifically they are processes for the characterisation of sequential decision problems in which the decision-makers choose an action in the "state" (of a system) occupied at any decision "epoch" (fixed point in time) according to a decision rule or policy. *Dynamic programming* techniques are the most commonly used approach for the solution of these problems and are concerned with devising algorithms to compute an

optimal control policy to a given Markov decision process. Cheng *et al.* (2004) presented a review and comparison of optimal control and stochastic programming techniques. The authors noted that stochastic programming is more suitable for solving long term strategic planning problems, such as capacity planning, with a relatively few number of periods and scenarios, while stochastic optimal control, on the other hand, works better for operational control problems such as production and inventory control. An example of such work is Cheng *et al.* (2003) who posed the representation of multistage stochastic problems as discrete time Markov decision processes with recourse and suggested their possible solution using a dynamic programming strategy. Discussing the previous work, Jung *et al.* (2004) noted that while such a strategy was found to be conceptually very attractive, it was limited computationally by the effects of "state" dimensionality and the presence of constraints which involve variables from different stages, as is the case with inventory balances in planning problems. The authors (Jung *et al.*, 2004) proposed a simulation-based optimisation approach for supply chain management under demands uncertainty in which they combine deterministic mathematical programming planning and scheduling formulations with discrete event simulation and employ Monte-Carlo simulation to account for various uncertainties. The approach demonstrated much promise for applying combined simulation/mathematical-programming approaches for the treatment of planning problems by leveraging the strengths of both approaches.

Real-option-based valuation (ROV) frameworks for hedging under uncertainty have also been applied to planning in the process industries. This concept is based on arbitrage free pricing (financial option pricing theory) and risk-neutral valuation (risk free-rate of return), and presents an alternative to traditional NPV analysis. ROV replaces the rate of return with a risk-free rate of return, and the true probability distribution (of the uncertain parameter) with a risk-neutral probability. A recent application is that of Gupta and Maranas (2004) where they proposed a Real-Options-based framework for strategic decision making under uncertainty and presented a number of illustrative examples including an application to supply chain planning under demand uncertainty. A comparison with traditional NPV analysis

showed that considerable monetary savings can be achieved though the application of ROV frameworks.

2.4. Concluding Remarks

In Section 2.1, the works relating to planning and scheduling in the biopharmaceutical industry were presented. Few applications of planning and scheduling of bioprocessing have been considered in the literature. Of those applications most were found to focus on the short term scheduling of bioprocesses, and with a few exceptions were limited to commercial simulation tools directed at the biopharmaceutical industry. While such simulation approaches have had some success in aiding decision-making in the biopharmaceutical industry they are reported to fall short when it comes to production planning, where the combinatorial problem of the optimal sequencing and timing of campaigns is required along with the optimisation of related production variables such as inventory and changeover costs. There was found to be a distinct lack of mathematical programming works published on planning and scheduling in the biopharmaceutical industry, particularly on production planning.

In Section 2.2, the problem of production planning in the process industries which shares many similar features to that of the biopharmaceutical industry was reviewed, while in Section 2.2.1, short and medium term planning works in the process industries were presented. A vast number of works on production planning and aggregate planning works have been presented in the past, many of which have been applied within the closely related pharmaceutical industry which shares many of the features of the biopharmaceutical production planning problem, however none have been applied specifically to the biopharmaceutical planning or encompass all the characteristic features of the problem.

Given the shortcomings of simulation tools and industrial rule based methods reportedly used within the biopharmaceutical industry, and the lack of any distinct models within the process industry literature encompassing all the features of the biopharmaceutical planning problem, Chapter 3 presents a mathematical

programming formulation for the medium term planning of biopharmaceutical manufacture incorporating the characteristic features of the production planning problem in the biopharmaceutical industry.

In Section 2.3, the problem of production planning under uncertainty was introduced and relevant work in the area reviewed. In the first part, Section 2.3.1, some of the key issues and relevant works in the biopharmaceutical manufacturing industry were presented. Most of the work presented was aimed at demonstrating the impact of uncertainty on biopharmaceutical manufacture and evaluating the performance of different operating strategies under uncertainty. However there did not appear to be any work in the bioprocess literature which could determine optimal operating strategies under uncertainty, this paucity was also true for both planning and scheduling under uncertainty.

In Section 2.3, approaches for tackling optimisation under uncertainty were reviewed and relevant applications to planning under uncertainty within the process industry literature presented. The majority of works for planning under uncertainty were based on stochastic programming techniques most notably two-stage programming, which when applied to practical sized problems gives rise to large-scale combinatorial optimisation problems. Many efficient solution approaches for the solutions of these problems, some of which were general while others were more problem specific. The majority of stochastic programming approaches were aimed at tackling demand uncertainty in the medium term or investment and capacity related decisions in the longer term. However, there did not appear to be any relevant models tackling the type of uncertainty faced in the biomanufacturing industry such as variable fermentation titres, adding to the lack of deterministic planning models aimed at tackling production planning in the biopharmaceutical industry. Hence, in Chapter 4, a two-stage programming approach for medium term planning under uncertainty is presented along with a hierarchical algorithm for the problem's efficient solution.

Alternative techniques for optimisation under uncertainty were also reviewed. Aimed at providing more computationally efficient approaches without forgoing solution quality, a number of approaches including chance constrained programming, fuzzy

programming, real-options–based modeling and dynamic programming have been applied to production planning under uncertainty in the process industries with much success. But again there is a distinct lack of relevant work for the biopharmaceutical industry. Hence, in Chapter 5, an approach based on the concepts of chance constrained programming is presented as an alternative to traditional multi-scenario type stochastic programming techniques.

In Section 2.1, a number of works based on discrete event simulation techniques were presented as decision-making aids for the biopharmaceutical industry, however apart from the work of Rajapakse *et al.* (2005), which focuses on the product portfolio problem, there appears to be a paucity of work which aid the decisions related to the long term strategic problem of capacity planning. Mathematical programming approaches aimed at tackling long term strategic planning problems were discussed in Section 2.2.2 and Section 2.3.2. A number of these works tackled the problem of long term capacity planning in the pharmaceutical industry. Some focused on the product portfolio problem, while others focused on meeting the long term demands given the considerable uncertainty associated with the long term timescale. Generally, most of the work focused on developing detailed models and algorithms for the representation and solution of such problems. In Chapter 6, a mathematical programming approach for long term capacity analysis in the biopharmaceutical industry is presented where the focus is the representation of some of the characteristic features of the long term production planning problem in biopharmaceutical manufacturing along with a methodology for the quantification of different operating strategies (through multi-objective optimisation techniques) in the long term time-scale. In Chapter 7, a commercialisation plan is presented which may serve as a good starting point for biomanufacturers wishing to incorporate simulation-based optimisation approaches in their decision-making.

Chapter 3

Deterministic Medium Term Planning of Biopharmaceutical Manufacture

3.1. Introduction

The work presented in this chapter addresses the biopharmaceutical manufacturing challenge of optimal planning of production i.e. the determination of the optimal amounts to be produced and the optimal sequence of products needed in order to maximise cost-effectiveness of a multiproduct facility. The proposed model aims to tackle problems over a "medium term" time scale of 1-2 years. In the formulation presented a multiproduct biopharmaceutical facility is required to satisfy a set of customer demands while minimising operating, storage and changeover costs. A penalty is introduced for late delivery of product. The problem formulation presented in this work is based on the capacity planning model developed by Papageorgiou *et al.* (2001) which embodies various features of the pharmaceutical industry. The production constraints are defined so as to provide a more accurate representation of production time since this will be a key need in medium term planning as opposed to the case of longer term planning where a more relaxed description may be adequate. The production constraints address the issue of the long lead times (duration of setup and cleaning at the start of a new campaign) introduced during campaign changeover

which can have a great impact on the overall plant capacity utilisation. The campaign planning problem is formulated as an MILP problem whereby a discrete time representation is used and production is represented as a rate.

While a large proportion of production planning problems in the biopharmaceutical industry are adequately represented by assuming negligible intermediate storage post harvest and prior to purification, in many cases industrial practice allows for flexible intermediate storage. Examples include perfusion processes where one fermentation batch is harvested in a "feed and bleed" mode continuously feeding the fermenter with nutrients and harvesting for pending downstream purification. Cases also exist where fermentation throughputs differ to those of the corresponding downstream purification. This can arise when contract manufacturers are required to fit processes to existing equipment with fixed sizes. Here the harvest may be divided into sub-batches which are processed downstream when equipment becomes available. To allow for such intermediate storage and differing throughputs between harvest and purification a similar dual production constraint representation to that of the capacity planning model of Gatica *et al.* (2003) was implemented.

To demonstrate the approach developed in this chapter two examples based on industrial data were solved. The first example is that of a multiproduct production planning problem involving a typical number of mammalian cell products manufactured over a 1 year production time horizon. The second example again involves mammalian cell products but this time with suite-specific manufacturing considerations and differing production throughputs, the products are manufactured over 1.5 year time horizon. The results from both examples are compared with those obtained using an industrial rule-based approach.

3.2. Problem Features

The problem of biopharmaceutical production planning is characterised by some unique features of biomanufacturing. These features and their role in production planning are discussed below:

3.2.1. Biomanufacturing and Plant Capacity

The problem of interest in this chapter is planning of primary manufacturing within multiproduct biopharmaceutical facilities. These facilities can have multiple suites or production lines and are usually divided further into rooms separating various sections of the manufacturing process e.g. upstream fermentation and downstream purification.

Plant capacity utilisation is an important issue in the biopharmaceutical industry and optimal planning of manufacture offers an opportunity to improve capacity utilisation (Mallik *et al.*, 2002). It has been estimated (Mallik *et al.*, 2002) that a typical new mammalian cell-culture facility would increase annual revenues by $380 million with a 25% increase in plant utilisation. Ransohoff (2004) estimates that the carrying costs (variable costs incurred by holding inventories) for a typical 500kg/year monoclonal antibody (mAb) facility working at 50% under utilisation are $2 - 3 million/month, while 50% under capacity based on oncology mAb pricing can result in an estimated loss of $40 – 50 million/month in operating profit. Hence optimising plant utilisation is crucial for both cost-effective manufacture and for maintaining competitiveness within the biopharmaceutical industry. It is likely to become even more crucial as generics enter the market in greater numbers (Coe, 2001).

3.2.2. Product Storage

Many biopharmaceutical industry products suffer from product instability (Li *et al.*, 1995) and hence must to be stored under specialised and costly storage conditions. Hence product shelf-life is a major concern in biopharmaceutical manufacture and can play an important role within production planning. Wilkins *et al.* (2001) reports that specialised storage methods such as cryopreservation enable manufacturers to de-couple steps in production processes by storing and transporting intermediates and products under defined, stable and validatable conditions, hence offering increased flexibility for scheduling and planning. Storage of harvested intermediate products can have an impact on product stability and result in shorter product lifetimes, making optimal intermediate storage strategies paramount to the realisation

of efficient capacity utilisation. Another important inventory issue is the very costly nature of manufacturing biopharmaceuticals. The high value of these products imposes a limit on the size of any product inventory held as this may constitute tying up working capital which is required elsewhere.

3.2.3. Regulations and Campaign Changeover

Validation within the highly regulated biopharmaceutical manufacturing industry is an expensive and time consuming process. Manufacturers are regulated to demonstrate the ability to reproduce consistently a process which meets predetermined specifications and quality attributes at various critical stages of the manufacturing process with a lot-to-lot consistency being realised (Lim *et al.*, 2004). These stringent regulations lead to rigorous cleaning and sterilisation between individual product batches as well as between new campaign start-ups. Contamination can lead to the introduction of long delays and unwelcome cost to the manufacturing process as a result of lost product due to batch failures. Long lead times typical in biopharmaceutical manufacture due to upstream process bottlenecks and the required validation processes are major motivations for manufacturing in long campaigns and avoiding frequent campaign changeovers. While on the other hand inventory cost, limited product lifetimes and multiple orders of a product constitute the necessity for campaign changeover. This presents a genuine decision making challenge for biomanufacturers.

3.2.4. Product Demand

Meeting demand dates in the biopharmaceutical industry is a highly sensitive issue due to the high value of the products involved. Mallik *et al.* (2002) estimate for example, that the lack of manufacturing capacity for Immunex's highly successful arthritis drug Enbrel cost the company more than $200 million in lost revenue in 2001. Companies must therefore strive to capture every day of revenue generation by ensuring an adequate supply of product. Customer demands within the biopharmaceutical manufacturing industry are typically the result of a negotiation whereby order quantity, delivery date and any variability on this is regulated by a

contract. Customers and manufacturers will agree on this taking into account existing capacity and goodwill. Penalties and manufacturer liability are usually agreed for late deliveries.

3.3. Problem Statement

A formal statement for the problem of campaign planning of biopharmaceutical facilities can be stated as follows.

Given:

- A set of products.
- A set of fermentation and purification suites.
- Production rates, lead times and production throughputs (correspondence factors).
- Product lifetimes, storage costs and storage capacities.
- Product demands, sales prices, and late delivery costs.
- Manufacturing and campaign changeover costs.
- Minimum and maximum campaign durations.

Determine:

- Campaign durations and sequence of campaigns.
- Production quantities along with inventory profiles.
- Product sales and late deliveries profile.

Objective:

- Maximise manufacturing profits.

3.4. Mathematical Formulation

A mathematical formulation composed of an objective function and constraints is derived in order to represent and solve the biopharmaceutical production planning problem. The mathematical formulation along with the modelling assumptions is explained in this section. One of the main assumptions employed in the development of the production constraints was the introduction of a continuous rate of production to represent the batch manufacture of biopharmaceuticals. In this each batch is treated as a "black box" as this captures the necessary level detail required by the problem's time scale (1 - 2 years). Figure 3.1 along with the following section explains the concept behind this.

The repeating period from *t1* to *t5* shown in Figure 3.1 as *EB* is the effective batch time. A continuous production rate r_p (batches per unit time) can be used to describe this repeating sequence of batches:

$$B = r_p T \tag{1}$$

where B is the amount produced and T is the total campaign duration.

Despite the fact equation (1) ignores the duration of the first batch, it can prove a valuable approximation in cases of planning over long timescales where there are a large number of batches and lead times (in this case the time it takes to generate the first batch of a campaign) are not particularly long. However in the case where there are not a sufficiently large number of batches being produced and a higher degree of accuracy is needed, the above rate approximation may not be acceptable as the lead time will skew the rate and may result in poor quality or infeasible plans.

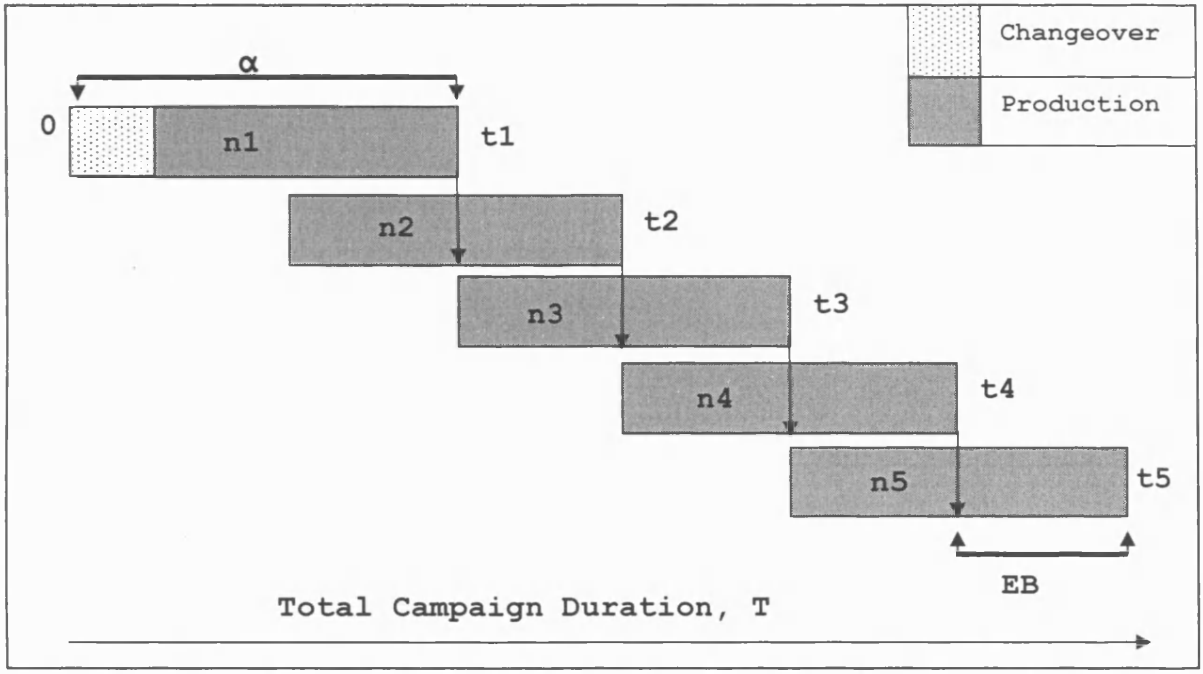

Figure 3.1: The black box approximation using an example Gantt chart of a process producing n = 5 batches of a given product p, where α is the duration of the first batch and EB is the effective batch time.

An extension to this rate constraint is proposed for more accurate representation of lead time α which is equal to the duration of the first batch of a campaign plus any start up time required for setup/cleaning.

The time taken for the production of n batches is described by constraint (2):

$$T = \alpha + (EB * (n-1)) \qquad (2)$$

where T is the total campaign duration, n is the total number of batches and EB is the effective batch time, the repeating period within the campaign.

The representation shown above is extended to allow for cases where there is a need for intermediate storage. The black box rate approximation shown in Figure 3.1 has been modified to incorporate the feature of intermediate storage post upstream fermentation and pre-downstream processing (purification). The concept of this modification is shown in Figure 3.2. The proposed biopharmaceutical production

planning formulation follows below. Figure 3.3 shows example configurations for the upstream production.

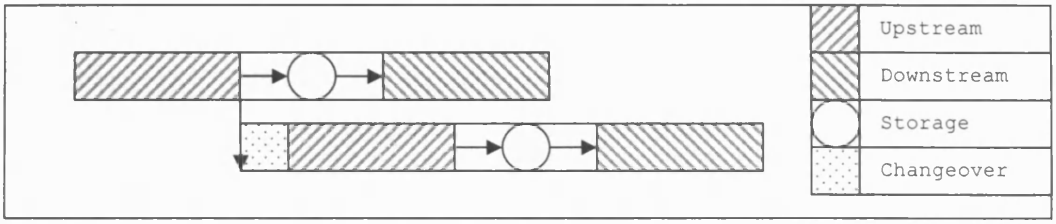

Figure 3.2: The extension of the black-box model allowing for intermediate storage.

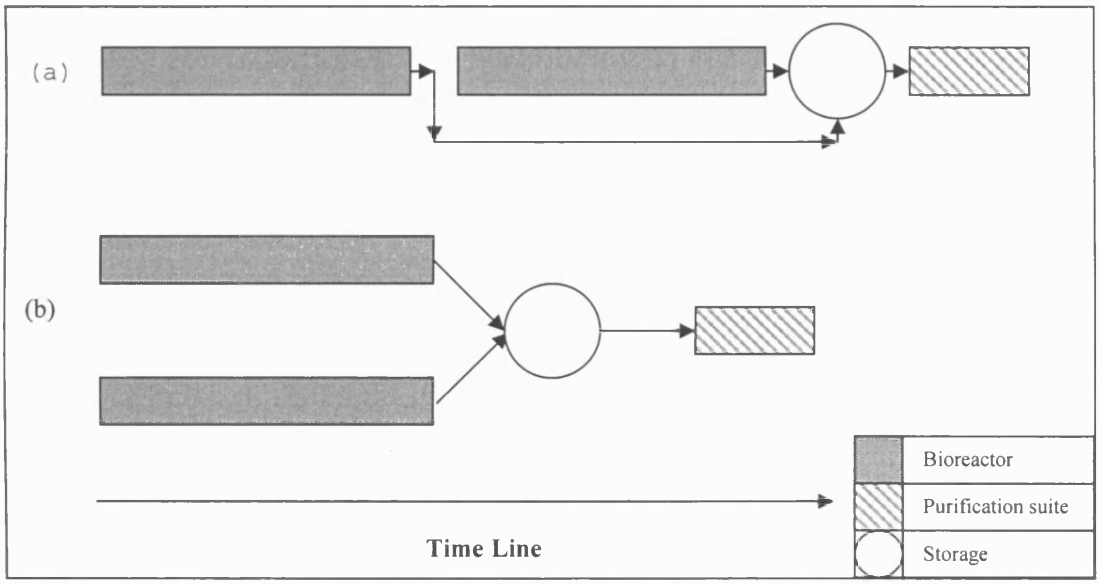

Figure 3.3: Two possible scenarios where pooling is used to accommodate the different throughputs of the upstream and downstream manufacturing capacities running either one (a) or two (b) bioreactor suites.

All products p undergo downstream manufacturing in a suite i and upstream manufacturing in a suite j over a time period t.

3.4.1. Production Constraints

As biopharmaceutical production takes place in individual manufacturing suites, it is separated into upstream and downstream by two rate equations as in the work of Gatica *et al.* (2003). Constraints (3) and (4) represent the production constraints for *crude*/intermediate product, and *final* product. Upstream production, CP_{ipt}, and downstream production, FP_{jpt}, are represented by continuous production rates for crude/upstream, CR_p, and final/downstream production, FR_p which are combined with their respective upstream and downstream lead times, α_p. This allows for set-up and cleaning time before the first batch of crude product is made. β_p allows for the time it takes for the necessary amount of crude product to be produced in order to produce one batch of final product, and to hence calculate the appropriate production times. Upstream production time, CT_{ipt}, and downstream production time, FT_{jpt}, show the duration of manufacture of each product p within each team period t. If a product p is selected for manufacture at a given suite i or j at time t a lead time, α_p, and/or β_p will only be included to that campaign duration to account for the setup and cleaning if binary variables Z_{ipt} and/or W_{jpt} are equal to 1 (denoting the start of a new upstream/downstream campaign).

$$CP_{ipt} = Z_{ipt} + CR_p(CT_{ipt} - \alpha_p Z_{ipt}) \qquad \forall i,p,t \qquad (3)$$

$$FP_{jpt} = W_{jpt} + FR_p(FT_{jpt} - \beta_p W_{jpt}) \qquad \forall j,p,t \qquad (4)$$

Binary variables Y_{ipt}, and U_{jpt} are introduced to denote whether or not a product p is manufactured in suite i or j at time t. In order to enforce the relevant production lead times constraint (5) is introduced. It enforces that Z_{ipt} in constraint (3) will only be activated if product p is not manufactured upstream in the previous time period t-1, i.e. it is the start of a new campaign upstream. While constraint (6) enforces that W_{jpt} in constraint (4) will only be activated if product p is not manufactured downstream in the previous time period t-1, i.e. it is the start of a new campaign downstream.

$$Z_{ipt} \geq Y_{ipt} - Y_{ip,t-1} \qquad \forall i,p,t \qquad (5)$$

$$X_{jpt} \geq U_{jpt} - U_{jp,t-1} \qquad \forall j,p,t \qquad (6)$$

In order to represent the lack of a lead time when existing crude product is held in storage, constraint (7) enforces that if any crude product p is held in storage prior to downstream production/purification then the inclusion of a lead time β_p to the downstream production time will not happen. Hence the only instance in which W_{jpt} is equal to 1 is when both Z_{ipt} and X_{jpt} are equal to 1.

$$W_{jpt} \geq \frac{\sum_{i} Z_{ipt}}{card(i)} + X_{jpt} - 1 \qquad \forall j, p, t \qquad (7)$$

In order for the production constraints to capture the required campaign changeover considerations, constraints (8) and (9) ensure that at most one product p undergoes manufacturing in any given suite i or j at any given time period t. This is necessary for the effective operation of the new campaign selection/changeover variables in constraints (1-5).

$$\sum_{p} Y_{ipt} \leq 1 \qquad \forall i, t \qquad (8)$$

$$\sum_{p} U_{jpt} \leq 1 \qquad \forall j, t \qquad (9)$$

3.4.2. Timing Constraints

In some cases, manufacturers enforce minimum and/or maximum campaign lengths in order to maximise efficiency or to allow for relevant maintenance/slack. Constraints (10-13) represent the appropriate minimum and maximum production time constraints for both fermentation suites i and purification suites j, where CT_p^{min}, FT_p^{min}, are the minimum upstream and downstream campaign durations, CT_p^{max}, FT_p^{max}, are the maximum upstream and downstream campaign durations and H_t is the size of the time horizon. These constraints are only active if their respective binary variables Y_{ipt} and U_{jpt} are equal to 1, otherwise the production times are forced to 0.

$$CT_p^{\min} Y_{ipt} \leq CT_{ipt} \qquad \forall i, p, t \qquad (10)$$

$$CT_{ipt} \leq \min\left\{CT_p^{\max}, H_t\right\} Y_{ipt} \qquad \forall i,p,t \qquad (11)$$

$$FT_p^{\min} U_{jpt} \leq FT_{jpt} \qquad \forall j,p,t \qquad (12)$$

$$FT_{jipt} \leq \min\left\{FT_p^{\max}, H_t\right\} U_{jpt} \qquad \forall j,p,t \qquad (13)$$

3.4.3. Storage Constraints

The following constraints enforce an inventory balance for upstream and downstream production and forcing total downstream production to meet product demand. In constraint (14) the amount of crude product p stored at the end of the time period CI_{pt}, is equal to the amount at the previous time period CI_{pt-1}, plus the net amount produced during the time period CP_{ipt}, less the amount processed downstream FP_{jpt}, and the amount wasted due to the expired product shelflife CW_{pt}. In constraint (15) the amount of final product p stored at the end of time period FI_{pt}, is equal to the amount at the previous time period FI_{pt-1}, plus the net amount produced during the time period FP_{jpt}, less the amount sold S_{pt}, and the amount wasted due to the expired product shelflife FW_{pt}.

$$CI_{pt} = CI_{p,t-1} + \sum_i CP_{ipt} - (1/\lambda_p) \sum_j FP_{jpt} - CW_{pt} \qquad \forall p,t \qquad (14)$$

$$FI_{pt} = FI_{p,t-1} + \sum_j FP_{jpt} - S_{pt} - FW_{pt} \qquad \forall p,t \qquad (15)$$

The λ_p symbol represents a production correspondence factor which allows the specification of the respective throughputs of the crude (upstream fermentation) and final (downstream purification) production. λ_p may be an integer or a fraction depending on which production (upstream or downstream) throughput is greater. Factors greater than 1 denote a relatively greater upstream throughput, while factors less than 1 denote a relatively smaller upstream throughput e.g. a factor of 0.5 signifies that for every two upstream batches one downstream batch is produced.

The amount of upstream and downstream product stored over period t cannot be negative and should not exceed the respective maximum available product storage capacities, C_p and F_p.

$$0 \le CI_{pt} \le C_p \qquad \forall p,t \qquad (16)$$

$$0 \le FI_{pt} \le F_p \qquad \forall p,t \qquad (17)$$

Both upstream and downstream product and final product are constrained by limited product lifetimes, the total amount of stored crude and final product p cannot be used after the next ζ_p or ρ_p time periods respectively.

$$CI_{pt} \le \sum_{j} \sum_{\theta=t+1}^{t+\zeta_p} FP_{jp\theta} \qquad \forall p,t \qquad (18)$$

$$FI_{pt} \le \sum_{\theta=t+1}^{t+\sigma_p} S_{p\theta} \qquad \forall p,t \qquad (19)$$

Constraint (18) ensures the lifetime of the crude product by enforcing that it is processed downstream in less than ζ_p time periods from when it is stored upstream, while constraint (19) ensures that final product is sold in less ρ_p time periods from when it is stored downstream.

3.4.4. Backlog Constraints

Late deliveries are undesirable, and hence a penalty Δ_{pt} is incurred for every time period t that a given batch of product p is late meeting a product demand D_{pt}. This penalty is minimised in the objective function.

$$\Delta_{pt} = \Delta_{pt-1} + D_{pt} - S_{pt} \qquad \forall p,t \qquad (20)$$

3.4.5. Objective Function

The strategic objective in this formulation is to maximise operating profit. This is represented by an objective function which is considered to be the difference between "total sales" with each batch sold at a price v_p, and "total operating costs" which include batch manufacturing costs of η_p per batch, changeover ψ_p per batch, storage σ_p per batch and ω_p per batch, late delivery penalties Δ_p per batch, and waste disposal costs τ_p per batch. All costs are in "relative monetary units (rmu)".

[Model MP]

Maximise

$$\text{Prof} = \sum_p \sum_t (v_p S_{pt} - \sigma_p SI_{pt} - \omega_p BI_{pt} - \Delta_p \Delta_{pt} - \tau_p (CW_{pt} + FW_{pt}) - \sum_i (\eta_p CP_{ipt} + \psi_p Z_{ipt}) - \sum_j (\eta_p FP_{jpt} + \psi_p X_{jpt})) \quad (21)$$

Subject to: constraints (1 – 20).

The complete formulation MP encompassing equations (1 – 21) corresponds to a mixed-integer linear programming (MILP) model.

3.5. Illustrative Examples

In this section two typical biopharmaceutical production planning problems are solved using the mathematical formulation presented in Section 3.3.

The data used was based on real industrial information which includes lead times (days), production rates (batches/day) and product demands (batches of product). These were extracted from industrial case studies (BioPharm Services Ltd, London, U.K; Farid, 2001). Commercial data such as sales prices, manufacturing and penalty costs were selected based on discussions with industrialists and are consistent with a recent review of the biomanufacturing industry by Ginsberg *et al.* (2002).

Both example problems were implemented in GAMS (1998) using the CPLEX/MILP solver with a 5% margin of optimality and were all performed on an IBM RS/6000 workstation.

3.5.1. Example 1: General multiproduct multisuite manufacture.

This first example encompasses the general features of the biopharmaceutical medium term planning problem and by comparison to industrial rule-based planning demonstrates the value of the proposed mathematical formulation. Example 1's problem definition and associated data are given below:

- A multiproduct facility with two fermentation suites and two purification suites. All production suites do not have a product specific manufacturing functionality. Figure 3.4 illustrates the product manufacturing routes for three products *P1, P2* and *P3*.

- Three "mammalian cell" products are assumed (P1-P3), with one or two product orders each.

- A one year production horizon, with six time periods t each two months long, i.e. the production time horizon H_t, is 60 days long.

- The due date and demands profile is shown below in Table 3.1. Orders were assumed to be due at the end of each two month time period t. Early delivery is infeasible and late deliveries are penalised for each late period.

- Production rates, lead times and related parameters used in this example are shown in Table 3.2.

- Lead times α_p and β_p are in "days" and are assumed to be inclusive of seven days of product changeover related cleaning time.

Table 3.1: Demand profile for Example 1, showing each product demand and the time period it is due.*

Product	Time Periods					
	1	2	3	4	5	6
P1				6		6
P2			6			
P3		8			8	

*Note: All demands are in number of batches

Table 3.2: All relevant parameters used in Example 1.

Product	*Parameter data for Upstream production i*						*Parameter data for product p*		
	Production rate CR_p (batches/ day)	Lead time α_p (days)	Product lifetime, ζ_p (time periods)	Storage Capacity C_p (batch/ time riod)	Minimum campaign length CT^{min}_p (days)	Storage cost ρ_p (rmu/ batch)	Sales price υ_p (rmu/ batch)	Manufacturing cost η_p (rmu/ batch)	Waste Disposal cost τ_p (rmu/ batch)
P1	0.05	30	1	10	20	5	20	2	5
P2	0.045	32	1	10	21	5	20	2	5
P3	0.08	22.5	1	10	12.5	5	20	2	5
Product	Parameter data for Downstream production j						Parameter data for product p		
	Production rate, FR_p (batches/ day)	Lead time, β_p (days)	Product lifetime σ_p (time periods)	Storage Capacity F_p (batch/ time period)	Minimum campaign length FT^{min}_p (days)	Storage cost w_p (rmu/ batch)	Lateness penalty δ_p (rmu/ batch)	Changeover cost ψ_p (rmu/ batch)	Production factor λ_p
P1	0.1	40	3	40	10	1	20	1	1
P2	0.1	42	3	40	10	1	20	1	1
P3	0.1	34.5	3	40	10	1	20	1	1

Note that the sales prices and associated costs of production are identical for each product. This is so not to bias the production of any particular product.

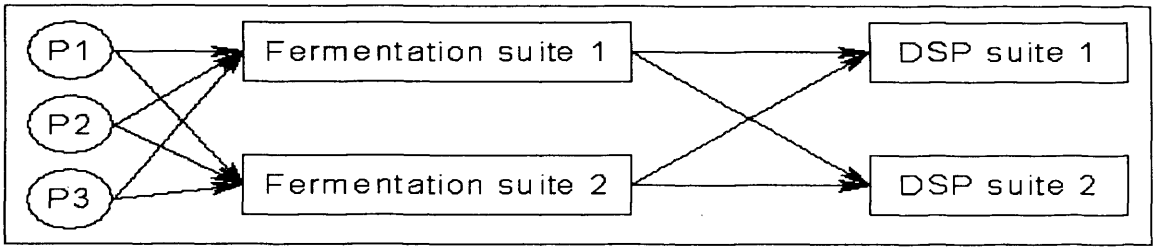

Figure 3.4: The functionality of the multisuite biopharmaceutical facility in Example 1.

Our proposed mathematical programming (MP) approach was compared with an industrial scheduling approach based on rules to demonstrate the effectiveness of the model. Traditionally much of the planning is done based on experience or on industrial rules, whereby typically products will be manufactured in singular long campaigns on a first come first served basis (earliest demand first), unless there is an obvious reason not to do so. This heuristic is summarised into three rules, as shown below:

1. Manufacture products in order of the product with the earliest demand first.

2. Allow a campaign to be split if manufacturing a product violates product lifetime constraints.

3. If a single campaign for a given product on a particular suite is unable to meet product demand on time, allow a campaign to be started on an alternative suite if available.

This industrial rule based (IRB) approach was used to develop a production schedule. A comparison of the results obtained by applying MP and IRB to Example 1 is shown in Table 3.3.

An objective function value of 487 rmu is achieved for MP which corresponds to a 72% profit margin, while IRB achieves an objective function value of only 430 rmu which corresponds to a 64 % profit margin. This was calculated as: the total profit as a proportion of the total sales. The difference in objective function is mainly

attributed to the 4 late batch penalties and the extra storage cost incurred by IRB. The results in Table 3.3 clearly show MP outperforming IRB in terms of punctuality and therefore profitability. Capacity utilisation is comparable, with IRB having a slightly higher capacity utilisation for both upstream and downstream (though at the expense of late batches).

Comparative graphical representations of the results are shown below in Figures 3.5, 3.6 and 3.7. Note that in Figure 3.5 each box/instance is colour coordinated to represent the particular product selected for manufacture. The *number of batches produced* is noted underneath each instance followed by the *production time in days* in brackets. The production suites are denoted *i* and *j* for upstream and downstream respectively.

Table 3.3: Comparison between solutions from the industrial rule based (IRB) approach and the proposed mathematical programming (MP) approach for Example 1.

Approach	Objective function (rmu)	Upstream Capacity Utilisation (%)	Downstream Capacity Utilisation (%)	Cost incurred as a result of late batches (rmu)
IRB	**430**	85	67	80
MP *	**487**	89	71	20

* Note: This problem was solved in 16 seconds.

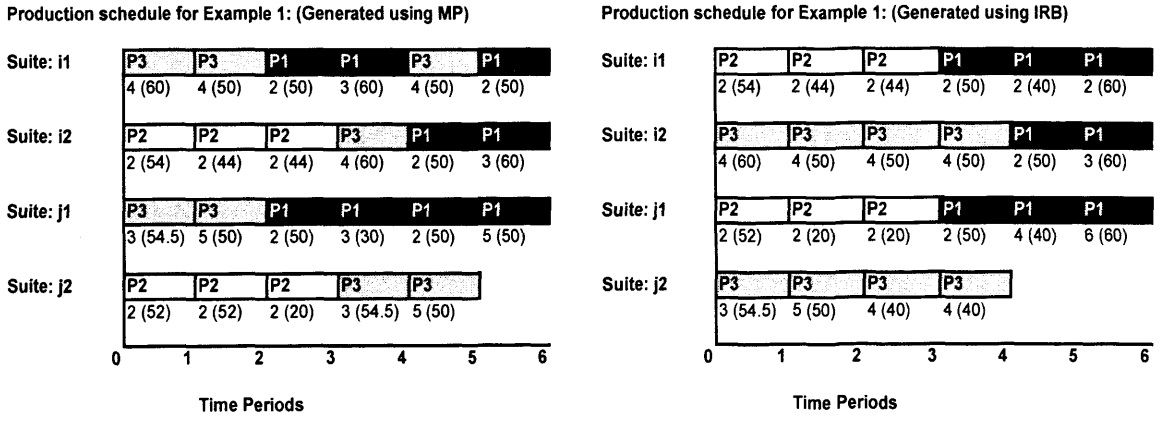

Figure 3.5: Production schedules for Example 1. Coloured boxes show which product is being manufactured in which suite, followed by number of batches produced and production time.

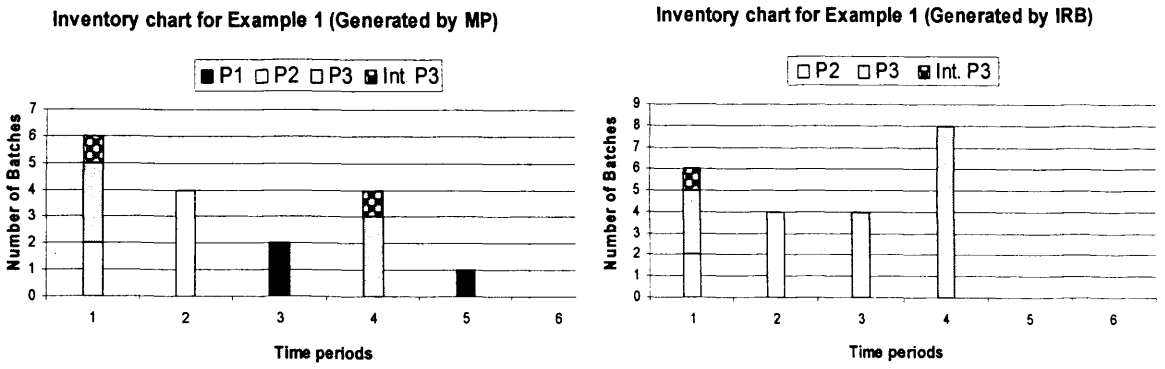

Figure 3.6: Inventory charts for Example 1. Each coloured bar shows how much product is being stored and in which time period.

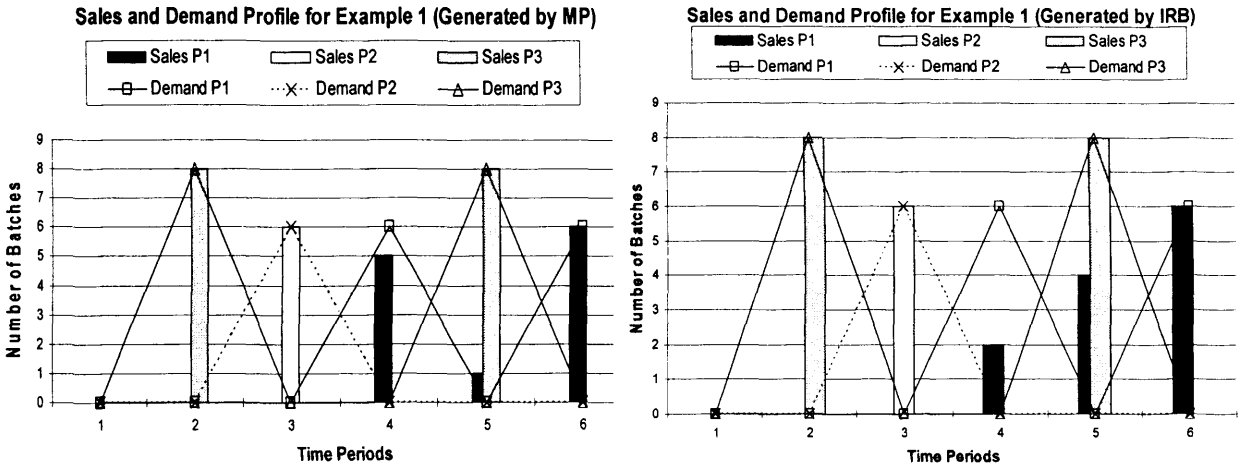

Figure 3.7: Sales & demand profiles for Example 1. Each coloured bar shows the sales of different products, while the respective demand is shown via lines and markers.

A number of points relating to Example 1 can be made:

- *Production plans* – Figure 3.5 shows the production schedules for both MP and IRB. In MP's production schedule product 2 is manufactured in one long campaign as it has only one order date, however due to the scattered demands there is value in a changeover for both products 1 and 3, thereby minimising inventory cost.

- *Campaign durations* – Table 3.4 shows that upstream plant capacity utilisation in MP's solution is particularly high at approximately 89 % (This is calculated as

the percentage of potential production time used for manufacture). It is the upstream capacity utilisation which is most commonly the manufacturing bottleneck in biomanufacture (Petrides *et al.*, 2004). This value of 89% is relatively high; the average biopharmaceutical industry capacity utilisation for biopharmaceutical manufacturing in 2003 was estimated to be 79% (Langer, 2004).

- *Inventory* – All intermediate and final product inventory for Example 1 is shown in Figure 3.6. In MP, intermediate storage is required for product 3 in time periods 1 and 4, as the crude product is stored until there is available downstream capacity in the next time period. The ability to reduce intermediate storage is beneficial since costly specialist storage conditions are usually required.

- *Demand Vs Sales* – The product demands and Sales for Example 1 are shown in Figure 3.7. All product orders are met in full and on time apart from one batch of product 1 which is due in period 4 but is delivered in period 5. There is no product wastage as production is forced to produce an integer number of batches and production correspondence is one to one.

3.5.2. Example 2: Suite specific manufacturing and differing production throughputs.

In this example another typical industrial biopharmaceutical planning problem involving intermediate storage is represented and solved using the mathematical formulation derived in this chapter. This example differs from Example 1 in that the upstream fermentation suites are product specific reflecting differing product manufacturing requirements and validation issues common to contract biomanufacturers. Secondly the product sales prices and manufacturing costs differ between products which results in the priority manufacturing of the more profitable products. Also *P3* and *P4* have differing upstream production throughputs, which reflect another issue a contract biomanufacturer may have to deal with. Finally the problem is solved over a larger 1.5 year time horizon in order to demonstrate the increased complexity that would result. Figure 3.8 shows the possible manufacturing routes of *P1* - *P4*.

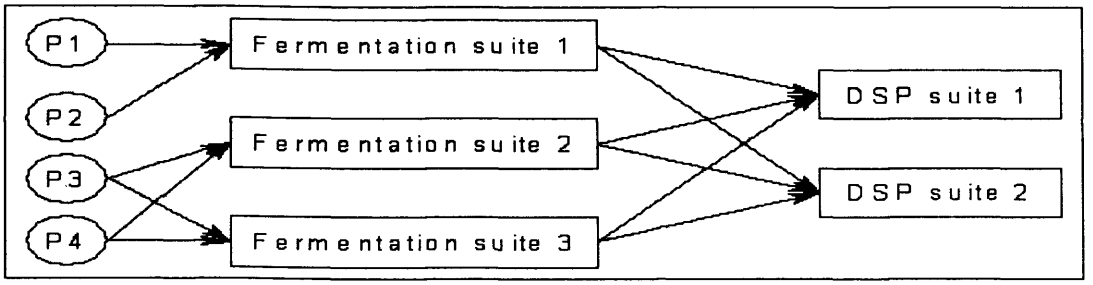

Figure 3.8: The functionality of the multisuite biopharmaceutical manufacturing in Example Problem 2.

The features described below characterise the example being tackled to illustrate the use of the proposed mathematical formulation. The problem definition and associated problem data are given below:

- A multiproduct facility with multiple production suites: three fermentation suites and two purification suites.
- Four "mammalian cell" products with one or two product orders (*P1, P2, P3* and *P4*).
- The due date and demands profile is shown below in Table 3.4, where orders are assumed to be due at the end of each time period t, where early delivery is infeasible and late deliveries are penalised for each time period they are late.
- Products P1 and P2 have a one to one correspondence of upstream and downstream throughput; i.e. a downstream purification batch is produced for every fermentation batch. However for products P3 and P4 there is a two to one correspondence due to a lower fermentation throughput for both products. This is represented by production correspondence factors which are shown in Table 3.5.
- A 1.5 year production horizon, with nine time periods t each two months long, i.e. the production time horizon H_t is 60 days long.

- Lead times are adjusted accordingly to represent the relevant throughput correspondences between upstream and downstream.

- Production rates, lead times and related parameters used in this example are shown in Table 3.5 below, sales prices and manufacturing costs are not identical which is realistic to industrial practice.

Table 3.4: Due date profile for Example 2:*

Product	Time Period								
	1	2	3	4	5	6	7	8	9
P1				6		4			4
P2		4					4		
P3									
P4		6		8	10				10

*Note: All demands are in number of batches

Table 3.5: Parameters used in Example 2.

Product	*Parameter data for Upstream production i*						*Parameter data for product p*		
	Production rate CR_p (batches/ day)	Lead time α_p (days)	Product lifetime, ζ_p (time periods)	Storage Capacity C_p (batch/ time period)	Minimum campaign length CT^{min}_p (days)	Storage cost ρ_p (rmu/ batch)	Sales price υ_p (rmu/ batch)	Manufacturing cost η_p (rmu/ batch)	Waste Disposal cost τ_p (rmu/ batch)
P1	0.05	30	1	10	20	5	25	5	5
P2	0.045	32	1	10	21	5	20	2	5
P3	0.08	22.5	1	10	12.5	5	17	1	5
P4	0.08	22.5	1	10	12.5	5	17	1	5
Product	Parameter data for Downstream production j						Parameter data for product p		
	Production rate, FR_p (batches/ day)	Lead time, β_p (days)	Product lifetime σ_p (time periods)	Storage Capacity F_p (batch/ time period)	Minimum campaign length FT^{min}_p (days)	Storage cost w_p (rmu/ batch)	Lateness penalty δ_p (rmu/ batch)	Changeover cost ψ_p (rmu/ batch)	Production factor λ_p
P1	0.1	40	3	40	10	1	20	1	1
P2	0.1	42	3	40	10	1	20	1	1
P3	0.1	44.5	3	40	10	1	20	1	0.5
P4	0.1	44.5	3	40	10	1	20	1	0.5

A similar IRB approach was used to generate a production schedule for Example 2. Table 3.6 shows a comparison of the main results obtained by IRB and MP, while Figures 3.9, 3.10 and 3.11 show graphical representations of the production schedules, inventory charts and sales & demand profiles.

Table 3.6: Comparison between solutions from the industrial rule based (IRB) approach and the proposed mathematical programming (MP) approach for Example 2.

Approach	Objective function (rmu)	Upstream Capacity Utilisation (%)	Downstream Capacity Utilisation (%)	Cost incurred as a result of late batches (rmu)
IRB	**384**	84	66	340
MP *	**539**	84	78	180

* Note: This problem was solved in 284 seconds.

MP's objective function of 539 rmu corresponds to a profit margin of approximately 50 %, while IRB's objective function of 384 a considerably lesser value of 35 %. The difference in profitability in this case is almost entirely due to the extra late demand penalty cost incurred by IRB. In the absence of the late demand factor, the resultant profits would be very comparable. The slightly lower downstream capacity utilisation of IRB is due to individual batches of product being processed downstream in bulk rather than when they are required to be processed, resulting in late deliveries. MP comfortably outperforms IRB in this case which is consistent with industrial perspectives that increasing size and complexity of planning problems limit the value of industrial rule based approaches.

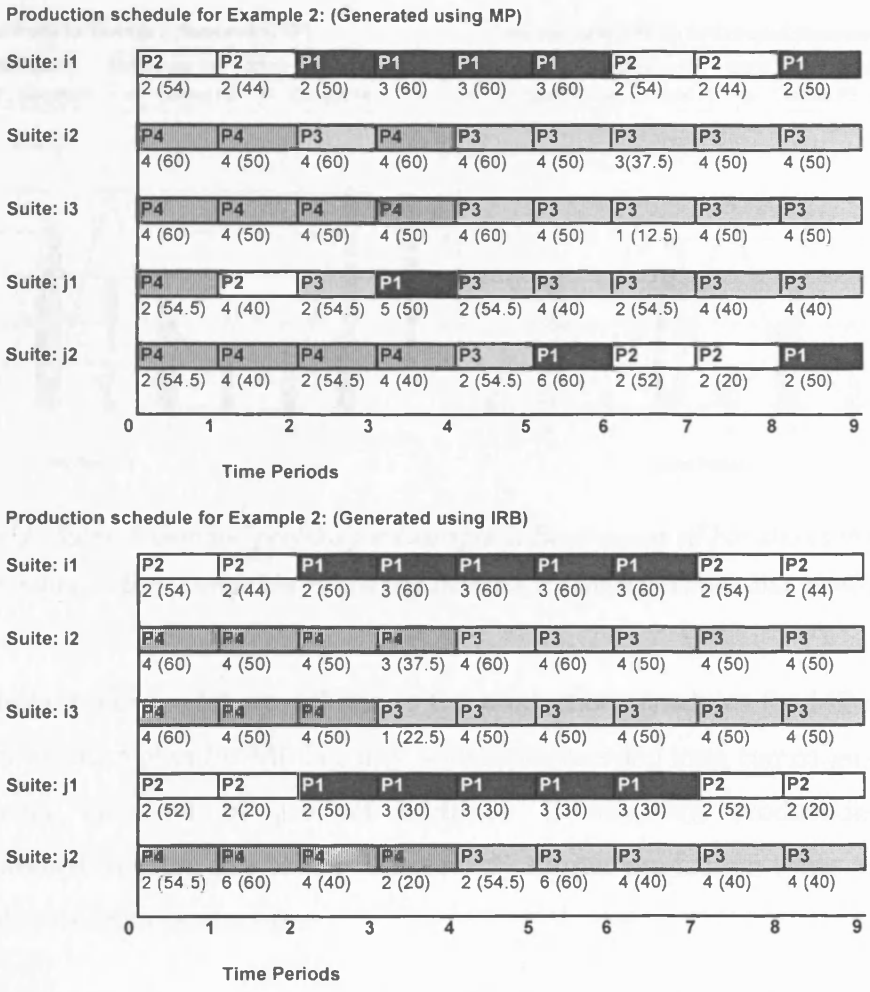

Figure 3.9: Production schedules for Example 2. Coloured boxes show which product is being manufactured in which suite, followed by number of batches produced and production time.

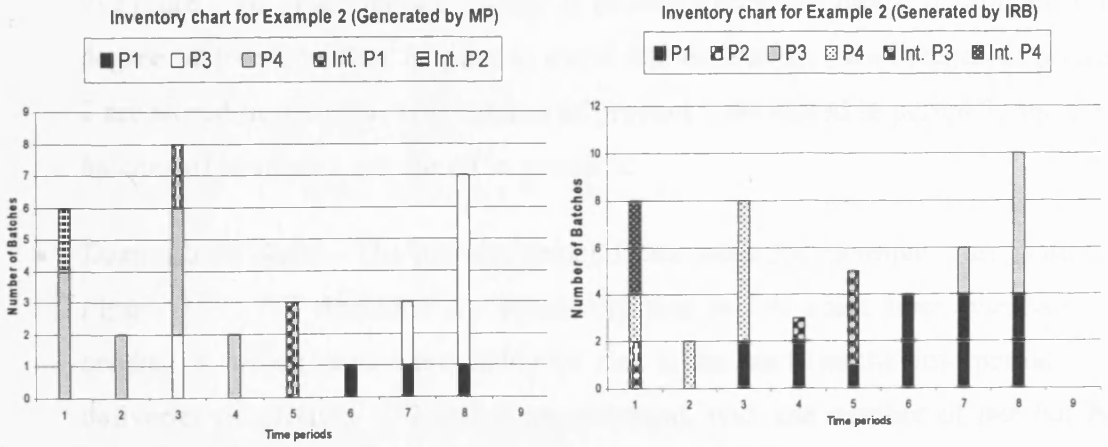

Figure 3.10: Inventory charts for Example 2. Each coloured bar shows how much product is being stored and in which time period.

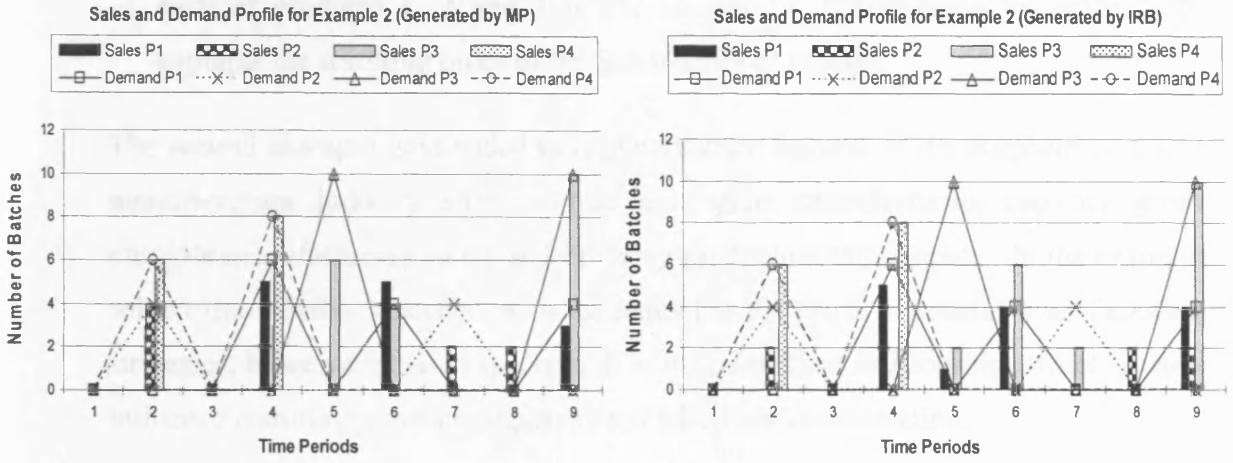

Figure 3.11: Sales & demand profiles for Example 2. Each coloured bar shows the sales of different products, while the respective demand is shown via lines and markers.

- *Production plans* – Figure 3.9 shows the production schedules for MP and IRB. The production plan for MP is a mix of changeovers and long campaigns in order to avoid violation of product lifetimes. Downstream production is not campaigned as often due to the considerably shorter production times associated with downstream production.

- *Campaign durations* - Plant capacity utilisation is approximately 84% which is higher than the industry average (79%).

- *Inventory* – All intermediate and final product inventory for Example 2 is shown in Figure 3.10. Intermediate storage is utilised giving the model a valuable extra degree of freedom, thus helping to avoid late deliveries. Two batches of product 2 are stored in period 1, two batches of product 1 are stored in period 3, and three batches of product 1 are stored in period 5.

- *Demands Vs Sales* - The product demands and sales for Example 2 are shown in Figure 3.11. All demands are eventually met in full apart from one batch of product 1, which would inevitably be met in the next (tenth) time period. Late deliveries of product 1, 2 and 3 are observed, with the number of late batches being 3, 2 and 4 respectively. This is attributable to the distribution of the product demands and the respective product profit margins. The relative profit margin on

each of products 1, 2 and 3 is 15, 16 and 14. Prioritisation by profitability explains the resulting order of the late batches of product.

The second example is intended to capture certain features of the biopharmaceutical manufacturing industry such as managing plant manufacturing capacity given multiple manufacturing suites and differing production throughputs. In the example solved the solution returned is in agreement with typical industrial manufacturing strategies; however certain aspects such as inherent client relationships which usually influence manufacturing strategies are not taken into consideration.

3.6. Conclusions

In this chapter a mathematical programming (MP) approach using an MILP formulation for medium term planning of biopharmaceutical manufacture has been presented. An improved formulation has been used to represent and solve two example problems based on real industrial data. Solutions to both examples generated using MP were compared to those generated by an industrial rule based (IRB) approach and demonstrated the value of the proposed approach. In both Examples 1 and 2 MP were shown to outperform IRB in terms of profitability, the difference in profitability can be mainly attributed to extra late batch penalties and storage costs due to the campaigning style employed. In the larger more complex Example 2 the profitability achieved by MP was considerably higher demonstrating the necessity for calculated decisions regarding campaign changeovers and inventory profiles. This confirms the ineffectiveness of IRB type approaches for solving larger more complex examples. In both examples, plant utilisation was high relative to typical industrial expectations, which in terms of manufacturing cost-effectiveness translates to improved profit margins.

3.7. Nomenclature

Indices

i	fermentation suites
j	purification suites
p	product
t, θ	time periods

Parameters

C_p	storage capacity of crude product p, batches
CR_{ip}	production rate of product p in suite i, batches per unit time
CT^{min}_p	minimum production time for product p at time period t
CT^{max}_p	maximum production time for crude product p
D_{pt}	demand of product p at time period t
F_p	storage capacity of final product p, batches
FR_{jp}	production rate of product p in suite j, batches per unit time
FT^{min}_p	minimum production time for product p at time period t
FT^{max}_p	maximum production time for final product p
H_t	available production time horizon over time period t
α_p	lead time for production of first batch of crude product p
β_p	lead time for production of first batch of final product p
ζ_p	life time of crude product p, in number of time periods t

σ_p life time of final product p, in number of time periods t

υ_p unit sales price for each batch of product p

η_p unit cost for each batch produced of product p

ψ_p unit cost for each new campaign of product p

δ_p unit cost charged as penalty for each late batch of product p

ρ_p unit cost for each stored batch of crude product p

ω_p unit cost for each stored batch of final product p

τ_p unit cost of disposing of a batch of product waste p

λ_p production correspondence factor for crude to final production of product p

Binary Variables

U_{jpt} 1 if final product p is produced in suite j over period t; 0 otherwise

W_{jpt} 1 if one or more campaigns are starting on i and j at any given time period t; 0 otherwise

X_{jpt} 1 if a new campaign of final product p is started in suite i over period t; 0 otherwise

Y_{ipt} 1 if crude product p is produced in suite i over period t; 0 otherwise

Z_{ipt} 1 if a new campaign of crude product p is started in suite i over period t; 0 otherwise

Continuous Variables

CI_{pt} amount of crude product p stored in suite i over period t

CT_{ipt} production time for product p on suite i at time period t

CT^{tot}_{it} total production time for suite i over period t

CW_{pt} amount of crude product p on suite i which is wasted over period t

FI_{pt} amount of crude product p stored in suite j over period t

FT_{jpt} production time for product p on suite j at time period t

FT^{tot}_{jt} total production time for suite j over period t

FW_{pt} amount of final product p on suite j which is wasted over period t

S_{pt} amount of product p which is sold over period t

$Prof$ operating profit

Δ_{pt} amount of product p which is late over period t

Integer Variables

CP_{ipt} amount of crude product produced in suite i over period t

FP_{jpt} amount of final product p produced in suite j over period t

Chapter 4

Medium Term Planning of Biopharmaceutical Manufacture using Two-Stage Programming

4.1. Introduction

In the previous chapter, an optimisation-based approach for medium term planning of biopharmaceutical manufacture was presented using a deterministic mathematical programming formulation which determines the optimal production plans for a biopharmaceutical facility given fixed/known parameters. The overall problem was formulated as an MILP model based on a discrete time representation.

The deterministic approach was compared to an industrial rule based approach and was able to achieve considerable improvement in operating profits. However, the model did not account for an inherent feature of biopharmaceutical manufacture which is the uncertain conditions associated with this environment, namely variable batch titres (yields), contamination rates and campaign length (Farid *et al.*, 2005). Schedules that do not account for these uncertainties are likely to lead to reduced operational performance. For example, variable fermentation titres (grams of product

per litre of broth) directly determine the number of batches required to satisfy product demands and hence impact directly on customer demand satisfaction and profitability.

Hence, focus of this chapter is the medium term planning of biopharmaceutical manufacture under uncertainty. The problem is formulated as a two-stage programming (multiscenario) MILP problem and an iterative algorithm is proposed for its efficient solution. This is tested on three illustrative examples of differing sizes and computational results are presented for the deterministic model, the full-space multiscenario model, a rolling horizon algorithm and the proposed iterative algorithm.

4.2. Problem Description

As was discussed in Section 3.2, the problem is characterised by some features fairly typical of process planning and scheduling problems such as late delivery penalties, multiproduct manufacture, inventory and capacity utilisation challenges, while other features are more specific to bioprocessing such as long lead times, specialist storage considerations and variable fermentation titres.

In recent work, (Farid *et al.*, 2005; Lim *et al.*, 2005; Biwer *et al.*, 2005) the impact of some common uncertainties on biopharmaceutical manufacture were explored through the use of Monte-Carlo (MC) simulations, and the fermentation titre was found to be the most critical driver affecting both the cost of goods and the facility throughput. Hence, the focus of this work is improving decision making given the aforementioned key source of uncertainty within the commercial biomanufacturing environment. In this chapter the deterministic model presented in section (3.2) is extended to allow for variable fermentation titres which are reflected as fluctuations in the production rate of product p, r_p.

As was mentioned previously, when tackling optimisation problems under uncertainty, parameters assumed to be uncertain are often represented by discrete outcomes using a multiscenario stochastic (two-stage) programming approach. This

approach is utilised by introducing three discrete outcomes (low, medium and high) for uncertain parameter r_{pk}, where k, the number of possible scenarios is a function of the number of products p and the number of outcomes o for uncertain parameter r_{pk}. The total number of scenarios is equal to o^p, hence in our problem the total number of scenarios is 3^p. This exponential relationship explains the combinatorial explosiveness that makes the solution of larger instances of this full-space multiscenario problem computationally intractable. This presents a genuine need for the efficient solution of this problem, ideally without sacrificing solution quality.

The overall problem of medium term planning of biopharmaceutical manufacture under uncertainty can be stated as follows:

Given:

- A set of products.
- Production rates and lead times.
- Product lifetimes, storage costs and storage capacities.
- Product demands, sales prices, and late delivery penalty costs.
- Manufacturing and campaign changeover costs.
- Minimum and maximum campaign durations.
- Outcomes and associated probabilities.

Determine:

- Campaign durations and sequence of campaigns.
- Production quantities along with inventory profiles.
- Product sales and backlog profiles.

Objective:

- Maximise expected manufacturing profit.

4.3. Mathematical Formulation

The formulation presented in this chapter is based on the deterministic medium term planning problem presented earlier (Section 3.2), here however the focus is shifted to tackling the impact of uncertainty.

The problem is formulated as a two-stage programming formulation. Index k is introduced to production rate, r_{pk}. Index k is also introduced to all continuous variables rendering them second stage (wait and see) variables. Binary variables for production, Y_{pt}, and changeover, Z_{pt} do not take on new index k as they are first stage decision variables (here and now) and allow for the selection of one operating schedule (production sequence) for all scenarios. The multiscenario formulation is presented below.

4.3.1. Production Constraints

Constraint (1) represents biopharmaceutical production. The number of batches produced of product p at time period t in scenario k, B_{ptk}, an integer variable, is calculated through production rate, r_{pk}, which is combined with production lead time, α_p. This lead time allows for the duration of the first batch of a campaign plus the set-up and cleaning time before the first batch is started. Production time, T_{ptk}, is the duration of manufacture of each product p within each time period t in scenario k. The logical incorporation of lead time is enforced by a binary variable Z_{pt}. If a product p is selected for manufacture at time t a lead time, α_p, will only be included in that campaign duration to account for the setup and cleaning if Z_{pt} is equal to 1 (denoting the start of a new campaign).

$$B_{ptk} = Z_{pt} + r_{pk}(T_{ptk} - \alpha_p Z_{pt}) \qquad \forall p,t,k \qquad (1)$$

Binary variable Y_{pt}, is introduced to denote whether or not a product p is manufactured at time t. In order to enforce the correct activation of binary variable Z_{pt}, constraint (2) is introduced. It enforces that Z_{pt} will only be activated if product p is not manufactured in the previous time period t-1, i.e. start of a new campaign.

$$Z_{pt} \geq Y_{pt} - Y_{p,t-1} \qquad \forall p,t \qquad (2)$$

Constraint (3) enforces that at most one product p undergoes manufacturing at any given time period, t.

$$\sum_{p} Y_{pt} \leq 1 \qquad \forall t \qquad (3)$$

4.3.2. Timing Constraints

In some cases, manufacturers enforce minimum and/or maximum campaign lengths in order to maximise efficiency or to allow for relevant maintenance/slack. Constraints (4) and (5) represent the appropriate minimum and maximum production time constraints, where T_p^{min} is the minimum campaign duration, T_p^{max} is the maximum campaign duration and H_t is the size of the time horizon. These constraints are only active if Y_{pt} is equal to 1, otherwise the production times are forced to 0.

$$T_p^{\min} Y_{pt} \leq T_{ptk} \qquad \forall p,t,k \qquad (4)$$

$$T_{ptk} \leq \min\left\{T_p^{\max}, H_t\right\} Y_{pt} \qquad \forall p,t,k \qquad (5)$$

4.3.3. Storage Constraints

The following constraint enforces an inventory balance for production and forces production to meet demand. In constraint (6) the amount of product p stored at the end of the time period t in scenario k, I_{ptk}, is equal to the amount stored at the previous time period t-1, $I_{p,t-1,k}$, plus the net amount produced during the current time period t, B_{ptk}, less the amount sold, S_{ptk}, and the amount of product wasted, W_{ptk} at the current time period t.

$$I_{ptk} = I_{p,t-1,k} + B_{ptk} - S_{ptk} - W_{ptk} \qquad \forall p,t,k \qquad (6)$$

Constraint (7) bounds the amount of product p stored over period t in scenario k so as not to exceed the maximum available product storage capacity, C_p.

$$I_{ptk} \leq C_p \qquad \forall p,t,k \qquad (7)$$

In constraint (8) stored product is constrained by limited product lifetimes, whereby any product stored during time period t cannot be sold after the next ζ_p time periods.

$$I_{ptk} \leq \sum_{\theta=t+1}^{t+\zeta_p} S_{p\theta k} \qquad \forall p,t,k \qquad (8)$$

4.3.4. Backlog Constraints

Late deliveries are undesirable, and hence a penalty Δ_{ptk} is incurred for every time period t that a given batch of product p in scenario k is late meeting a product demand D_{pt}. This is represented by constraint (9). Late batches are penalised in the objective function.

$$\Delta_{ptk} = \Delta_{p,t-1,k} + D_{pt} - S_{ptk} \qquad \forall p,t,k \qquad (9)$$

4.3.5. Objective Function

The strategic objective in this formulation is to maximise expected operating profit, *Eprof*. This is represented by an objective function which is considered to be the difference between "total sales" with each batch sold at a price v_p, and "total operating costs" which include the batch manufacturing cost at η_p per batch, changeover cost at ψ_p per batch, storage cost at ρ_p per batch and late delivery penalties of δ_p per batch. All costs and prices are in relative monetary units (rmu). All variables in the objective that contain index k are weighted by the probability of the occurrence of that scenario, $prob_k$.

[Model FULL]

Maximise

$$\text{Eprof} = \sum_p \sum_t \sum_k \text{prob}_k(v_p S_{ptk} - \eta_p B_{ptk} - \rho_p I_{ptk} - \delta_p \Delta_{ptk}) - \sum_p \sum_t (\psi_p Z_{pt}) \qquad (10)$$

Subject to: constraints (1 – 9).

The complete formulation FULL encompassing equations (1 – 10) corresponds to a mixed-integer linear programming (MILP) model. A specialised iterative solution approach is proposed in the next section.

4.4. Solution Methodology

Solving realistic size problems as full-space multiscenario problems often results in large scale MILP problems unsolvable in a realistic time scale by traditional branch and bound methods (this will be demonstrated in the following section 4.4). This presents the need for more efficient solution procedures. The algorithm proposed in this chapter is based on a similar concept to that introduced in the work of Werner and Winkler (1995). They present a heuristic algorithm with two parts; a constructive and an improvement part. The algorithm uses heuristic insertion rules in order to construct a feasible schedule for the job-shop problem and iteratively improves the schedule by using a heuristic search method which utilises insights derived from the problem's solution structure. The concept of constructing a preliminary schedule using a first stage and the iterative improvement of it in a second stage has been applied to industrial batch scheduling by Roslof *et al.* (2001), Mendez and Cerdá (2003) and most recently by Castro *et al.* (2006).

Each of the aforementioned works utilise the construction improvement concept for the efficient solution of large scale deterministic formulations. Here, a construction/improvement algorithm for the efficient solution of the large scale two-stage, multi-scenario, mixed integer linear programming (MILP) model detailed in the previous section 4.2 is presented. The proposed algorithm, CON/IMP, is composed of the following steps:

Step 1 - Construction (CON):

(i) Select order of insertion of products using random or heuristic rules.

(ii) For the selected product, p^*, expand r_{p^*} to $r_{p^*,k}$ while other products remain as mean value, $\bar{r}_p$.

(iii) Solve reduced two-stage model (FULL). Fix binary variables $Y_{p^*,t}$ and $Z_{p^*,t}$.

(iv) Reset $r_{p^*,k}$ to mean value, $\bar{r}_p$.

(v) If all products are considered go to step 2 (i), else insert next product, p^*: Go to step 1 (ii).

Step 2 - Improvement (IMP):

(i) Using random or heuristic rules, select, n, products to be released by unfixing their binary variables while keeping fixed the binary variables of the remaining products fixed to previous solution.

(ii) Construct reduced two-stage model (FULL) with o^n scenarios (with only the variables of the n selected products being scenario dependant).

(iii) Solve reduced two-stage model (FULL). Fix binary variables of released products.

(iv) Repeat (i), (ii) & (iii) until convergence is achieved.

(v) Run Monte-Carlo simulation to validate solution/schedule.

In the first step (CON) of the algorithm a schedule is constructed by way of sequential selection, optimisation and fixing of binary variables. The production schedule is constructed by consecutive insertion of products where the number of construction/ insertion steps is equal to the total number of products to be produced. For example, if the first product to be selected is $p1$, the production rate for $p1$, r_{p1}, becomes $r_{p1,k}$ as different discrete outcomes for production rate uncertainty are introduced, this means that the total number of scenarios k is equal to the total number of discrete outcomes, o^1, a linear relationship which replaces the exponential relationship encountered in the full space problem, o^p. After the reduced problem is

solved the binary variables associated with the *p1*, $Y_{p1,t}$ and $Z_{p1,t}$ are fixed and parameter $r_{p1,k}$ is reset to mean value, $\bar{r}_p$. These steps are repeated until the binary variables for all products are fixed and a full schedule has been constructed. The order of insertion may influence the quality of the solution obtained at the end of the construction stage, however this issue is averted by the introduction of the improvement stage, the second step of the algorithm. The solution schedule can be evaluated at this point, allowing the decision maker to decide if they wish to continue to the next step, as the current solution may be of sufficient quality.

In the second step (IMP) of the algorithm, *n* products are released iteratively in a bid to improve the solution achieved at the end of the first "construction" stage. *n* products are selected for release whereby the binary variables for the selected products are unfixed and the mean production rates replaced with uncertain rates resulting in o^n scenarios. For example, for $n = 2$, and $p = 1$ & 2, two products *p1* and *p2* are released, r_{p1} is set to $r_{p1,k}$ and r_{p2} set to $r_{p2,k}$, which results in a considerable reduction in problem size, o^2 instead of o^p where *p* is the total number of products. After this reduced problem is solved, parameters $r_{p1,k}$ and $r_{p2,k}$ are reset to the mean value, $\bar{r}_p$ and their associated binary variables are refixed. This process is continued iteratively, selecting *n* products randomly at each iteration until convergence is reached.

Convergence is defined as *SU* consecutive iterations with no change to the solution schedule. Finally solutions schedules are evaluated via Monte-Carlo (MC) simulation. MC will be discussed further in the following section.

4.5. Illustrative Examples

Three examples of differing size are solved to illustrate the applicability of the proposed construction/ Improvement algorithm (CON/IMP). The examples are solved for two different variabilities for uncertain parameter r_p, +/- 10% and +/- 20%. The results achieved using CON/IMP are compared with those achieved by the

deterministic model (DET) which differs from the formulation presented in this work only in that it does not contain the index k (introduced to allow for uncertain production rates) and hence assumes mean values for the uncertain parameter r_p, the full-space, two-stage programming model (FULL) presented in this work, and a rolling horizon algorithm (RH).

In the implementation of CON, the order in which products are selected for insertion is decided by using either random or heuristic rules. In this work, products are inserted in numerical order 1, 2, 3...n. During the improvement step (IMP), two products are randomly selected for release at each iteration (the number of products selected for release can be decided by the user, however in the authors' personal experience keeping this number as low as possible is advised for reasonable solution times). The selection of an insertion approach for CON and the number of products to be released in the IMP step is based on user experience. For convergence of the IMP step, the criterion $SU = 50$ is used in all example problems.

We also compare our algorithm with an iterative algorithm (RH) based on the concept of rolling horizons (Pinedo, 2002). The full-space, two-stage programming model is solved iteratively, whereby at each iteration, i, only a subset of T time periods, t, is solved. In the first iteration, i, the subproblem is solved for (i $(T\text{-}1)$) time periods, and the binary variables for (i $(T\text{-}1)$ + 1 - T) are fixed. The algorithm proceeds in this manner until all time periods, t, have been solved. The number of time periods in the subset, T, can be chosen by the decision maker (whereby the larger the value of T the longer the solution time and the higher the likelihood of an achieved solution being optimal). Figure 4.1 shows a diagrammatic representation of the algorithm. A value of T = 3 is used in all example problems.

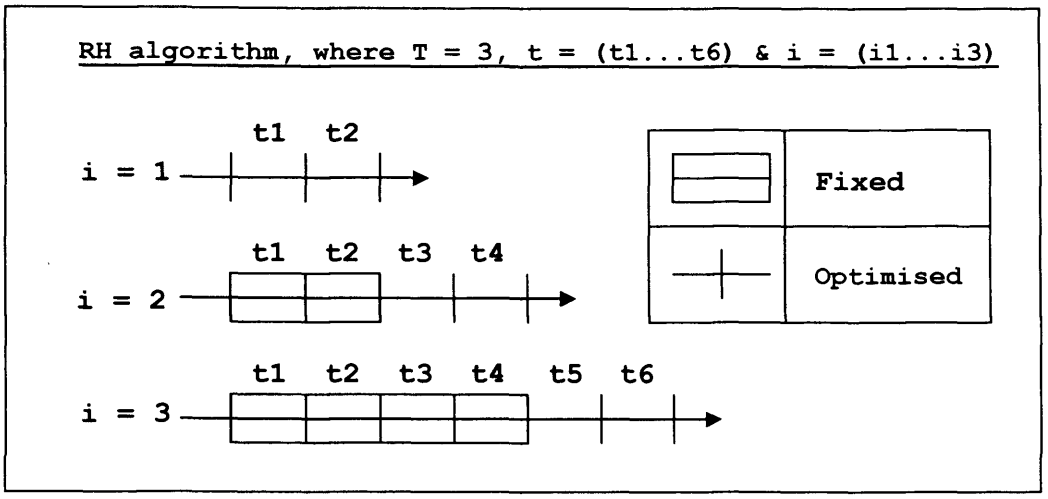

Figure 4.1: Iterations, i: 1 - 3 of the rolling horizon algorithm (RH), where t is the number of time periods to be solved for and T is the subset of time periods.

Monte Carlo (MC) simulation is used in order to better quantify the impact of variability on the deterministic schedules, as well as for the validation of the quality of solution schedules and thus the realistic expected performance. A number of simulation loops are setup in GAMS post model solution to create an improved approximation of the probability distribution assumed for uncertain parameter r_p. This presents an opportunity for the validation of the accuracy of the discrete probability distribution used in the mathematical programming model. Subsequent to the solution of each optimisation model the resulting scheduling decision variables Y_{pt} and Z_{pt} are fixed and MC simulation is conducted for uncertain parameter r_p. We compute the expected profit (MCPROF) until a convergence criterion is met. A minimum number of iterations are assumed, after which the standard error of the mean and an overall mean expected profit are computed at each iteration. When the standard error of the mean is less than 1% of the overall mean profit, the mean output value is considered to have converged (Hung *et al.*, 2006).

The data used in the Monte-Carlo simulation assumes a mean of r_p and a standard deviation of $unc*r_p$ where *unc* is a fractional value which signifies a symmetrical deviation representing the variability from the mean. For the two-stage programming model, three discrete outcomes (low, medium and high) are assumed and their equivalent probabilities are derived by truncation of a standard normal distribution

with mean $\bar{r}_p$ and standard deviation $unc*r_p$, by +/- 1 σ and the results are shown in Figure 4.2.

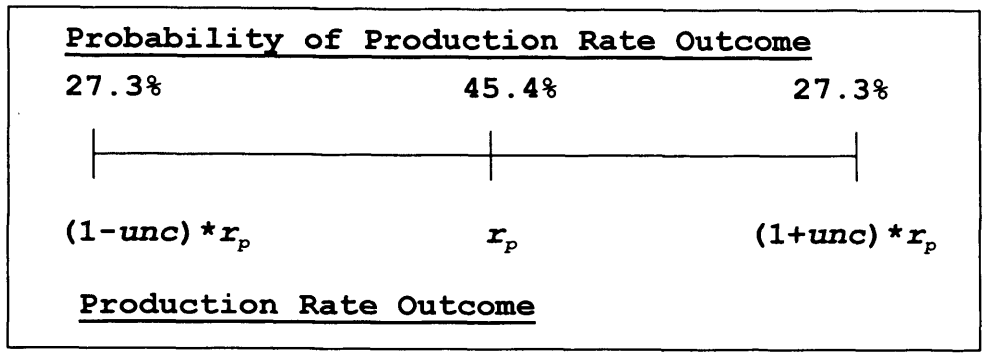

Figure 4.2: Equivalent discrete probability distribution of production rate r_p, where unc is the variability in r_p.

All problems were implemented in GAMS (Brooke *et al.*, 1998) using the CPLEX MILP solver, solving all problems to optimality. All runs were performed on a 1.8 GHz Pentium 4 PC with 512 MB RAM.

4.5.1. Example Problem Data

The sizes of each of the three examples tackled are shown below:

- Example 1: *three* products, *nine* time periods (1.5 year production time horizon).
- Example 2: five products, *ten* time periods (1.7 year production time horizon).
- Example 3: *ten* products, *eighteen* time periods (3 year production time horizon).

*Table 4.1: Demand profile for Example 1**

Product	*Time Period*								
	1	2	3	4	5	6	7	8	9
P1			3			2			
P2				3				5	
P3		2							5

*Note: All demands are in number of batches

*Table 4.2: Demand profile for Example 2**

Product	Time Period									
	1	2	3	4	5	6	7	8	9	10
P1					2					
P2										3
P3			2			2		2		
P4		2		3					2	
P5						3				

*Note: All demands are in number of batches

*Table 4.3: Demand profile for Example 3**

Product	Time Period																	
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
P1														4				
P2						3												
P3										2								
P4			2			3												
P5								2								3		
P6											3		4					
P7				3														
P8																3		
P9	2																	
P10																		3

*Note: All demands are in number of batches

The data associated with Examples 1 to 3 are presented below.

- A multiproduct facility producing p mammalian-cell-derived products is assumed, with one, two or three product orders for each product.

- A production horizon between 1.5 and 3 years long, split into t time periods each two months long, i.e. the production time horizon H_t, is 61 days long.

- The due date and demand profiles are shown in Tables 4.1 to 4.3. Orders were assumed to be due at the end of each two month time period t. Early delivery is assumed to be infeasible and late deliveries are penalised for each late period.

- Production rates, lead times and related parameters used in Examples 1 to 3 are shown in Table 4.4. Example 1 is assumed to include, P1-P3, Example 2, P1-P5, Example 3, P1-P10.

- All lead times α_p are in "days" and are each assumed to include seven days of product changeover related cleaning time.

Table 4.4: Parameters used in Examples 1-3, 1: P1-P3, 2: P1-P5, & 3: P1-P10

Product	*Parameter data*			*Sales price and Costs*			
	r_p (batches/ day)	α_p (days)	T^{min}_p (days)	Price/Cost	Symbol	Unit	Value
P1	0.05	30	20	Product lifetime,	ζ_p	time periods	3
P2	0.0909	28	11				
				Storage Capacity,	C_p	batch/day	6
P3	0.0625	32	16				
P4	0.05	30	20	Sales price,	υ_p	rmu/batch	10
P5	0.08	31	12.5				
				Manufacturing cost	η_p	rmu/batch	4
P6	0.05	30	20				
P7	0.0909	28	11	Storage cost	ρ_p	rmu/batch	0.2
P8	0.08	31	12.5				
				Late penalty	δ_p	rmu/batch	4
P9	0.05	30	20				
P10	0.0909	28	11	Changeover cost	ψ_p	rmu/batch	2

4.5.2. Example Problem Results

All three examples were solved using DET, FULL, CON, CON/IMP and RH at 10% and 20% production rate r_p variability and the computational results are shown in Table 4.5, while Figure 4.3 shows graphical representations of the achieved expected profits (MCPROF). A discussion on the impact of uncertainty, solution quality and solution times follows.

Table 4.5: Computational results for Examples 1-3.*

Computational Results		Optimisation				Monte-Carlo Simulation	
Indicator		**OBJ**		**CPU**		**MCPROF**	
% variability for r_p		**10**	**20**	**10**	**20**	**10**	**20**
Example 1	**DET**	108.5	108.5	1	1	**98.7**	**94.2**
	FULL	105.7	105.7	34	15	**105.8**	**101.1**
	CON/	105.5	105.5	1	1	**105.7**	**101.1**
	CON/IMP	105.8	105.8	20	15	**105.8**	**101.1**
	RH	105.7	105.7	10	7	**105.8**	**101.1**
Example 2	**DET**	109.5	109.5	1	1	**93.9**	**84.8**
	FULL	110.7	99.3	1330	2203	**100.3**	**89.0**
	CON	109.6	102.6	2	2	**94.0**	**85.1**
	CON/IMP	104.9	100.4	28	26	**100.3**	**89.4**
	RH	105.3	98.3	98	202	**100.3**	**87.3**
Example 3	**DET**	195.6	195.6	2.9	3.0	**179.2**	**152.6**
	FULL	-	-	-	-	-	-
	CON	193.8	195.8	8	8	**183.7**	**155.3**
	CON/IMP	195	195	40	39	**191.7**	**168.2**
	RH	-	-	-	-	-	-

*Note: Optimisation objective function (OBJ), Solution time in seconds (CPU) and Monte-Carlo simulation objective function (MCPROF); for results from DET (Deterministic model), FULL (the full space multiscenario problem), CON (the construction step), CON/IMP (Iterative construction/improvement algorithm) and RH (Rolling horizon algorithm).

The impact of uncertainty on operating profits is calculated as the percentage difference between the achieved profit in the absence of uncertainty and that achieved when introducing uncertainty via MC simulation. We calculate the impact for Examples 1, 2 & 3 to be a 9, 14 and 8% drop and a 13, 22 and 22% drop for the respective variabilities of 10 and 20%. This shows a significant negative impact on profits which increases with increasing variability and provides strong motivation and support for methods aiding decision-making under uncertainty in the biopharmaceutical industry. Table 4.6 shows the percentage improvement in solution quality of FULL, CON, IMP and RH over that achieved by the deterministic model.

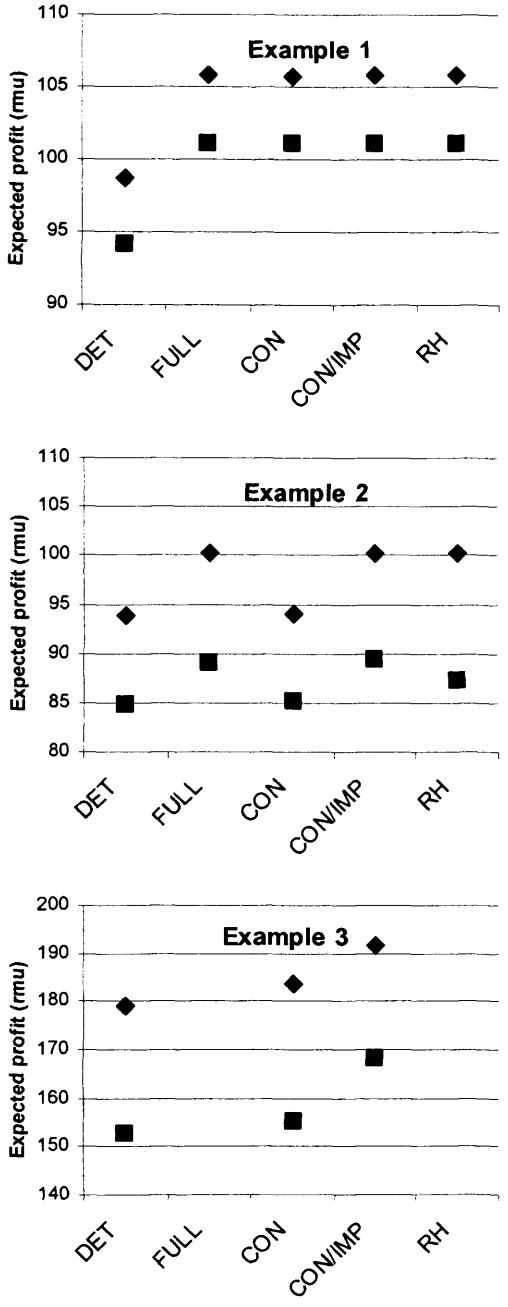

Figure 4.3: Graphical representations of achieved expected profits (MCPROF) for examples 1, 2, 3 and 4 using DET (deterministic model), FULL (the full space multiscenario problem), CON (the construction step), CON/IMP (Iterative construction/improvement algorithm) and RH (Rolling horizon algorithm), where ♦ represents 10% variability and ■ represents 20% variability.

Table 4.6 Percentage improvement in expected profit over the deterministic model solution for Examples 1-3.*

% variability for r_p		10	20
Example 1	**FULL**	7.2	7.3
	CON	7.1	7.3
	CON/IMP	7.2	7.3
	RH	7.2	7.3
Example 2	**FULL**	6.8	5.0
	CON	0.1	0.4
	CON/IMP	6.8	5.4
	RH	6.8	2.9
Example 3	**FULL**	-	-
	CON	2.5	1.8
	CON/IMP	7.0	10.2
	RH	-	-

DET (Deterministic model), FULL (the full space multiscenario problem), CON (the construction step), CON/IMP (Iterative construction/improvement algorithm) and RH (Rolling horizon algorithm).

FULL is able to able to solve Examples 1 and 2 to optimality but the projected exponential increase in problem size and hence solution time leads to the machine running out of memory and no solution being returned for Example 3 (1.8 GHz Pentium 4 PC with 512 MB RAM). Table 4.7 shows the number of scenarios generated in the full space multiscenario problem in each of the examples. While RH is able to make a considerable reduction in the computational requirements for Examples 1 and 2, the reduction in problem size achieved by the algorithm is not sufficient to obtain a solution for Example 3 as the exponential increase in problem size again proves too challenging for the hardware employed.

Table 4.7: Exponential relationship between the number of products and number of scenarios in the full space multiscenario problem (FULL).

Example	Number of Products, p	Number of Scenarios, k
1	3	27
2	5	243
3	10	59049

CON achieved differing degrees of improvement over DET throughout each of the three examples tackled in particularly modest timescales never exceeding 8 seconds. The CON/IMP algorithm is able to match the optimal solutions of both FULL and RH in Examples 1 and 2, while making considerable savings in solution time over FULL. In Example 3 both CON and CON/IMP are able to achieve considerable improvements over DET where both FULL and RH fail to achieve a solution. The solutions achieved by both CON and CON/IMP for Example 3 are all achieved within modest timescales never exceeding 40 seconds. The increase in solution time seen by CON/IMP is much closer to linear than exponential demonstrating its effectiveness for tackling larger and more computationally challenging problems.

The two-step iterative algorithm CON/IMP shows that by using step 1 CON, improved solutions can be achieved within particularly modest timescales (<8s), while step 2 IMP can make further improvements and is able to match solutions achieved by solving the full space problem within still relatively modest timescales (<32s). Considering the size of the largest example tackled, this demonstrates the exceptional reduction in problem size achieved by CON/IMP and value of this approach for two-stage programming problems. This method is envisaged to be of value in other applications of two-stage programming.

4.6. Conclusions

In this chapter, a mathematical optimisation-based framework for medium term biopharmaceutical manufacturing planning under uncertainty has been presented, and tested on three illustrative examples of different size and at different variabilities. The problems were all solved using a deterministic model (DET), the full-space two-stage programming model, a two-step rolling horizon algorithm (RH) and the proposed construction/improvement algorithm (CON/IMP). The impact of uncertainty on the solution schedules was quantified for both examples via Monte Carlo (MC) simulation. The results showed that CON/IMP consistently matched the results of FULL and RH while improving on DET for small and more modest sized

examples (1 and 2). While in the larger more challenging example (3) where both FULL and RH failed to achieve any solution, CON/IMP is still able to achieve considerable improvement on DET in particularly modest solution times.

4.7. Nomenclature

Indices

p	product
t, θ	time periods
o	outcomes
k	scenarios

Parameters

C_p	storage capacity of product p, batches
D_{pt}	demand of product p at time period t
r_{pk}	production rate of product p, batches per unit time in scenario k
H_t	available production time horizon over time period t
T^{max}_p	maximum production time for product p
T^{min}_p	minimum production time for product p
α_p	lead time for production of first batch of product p
ζ_p	life time of product p, number of time periods t
υ_p	unit sales price for each batch of product p
η_p	unit cost for each batch produced of product p

ψ_p unit cost for each new campaign of product p

δ_p unit cost charged as penalty for each late batch of product p

ρ_p unit cost for each stored batch of product p

SU numbers of iteration with no change to Y_{pt} during improvement phase

unc fractional deviation from the mean

Binary Variables

Y_{pt} 1 if product p is produced over period t; 0 otherwise

Z_{pt} 1 if a new campaign of product p is started in period t; 0 otherwise

Continuous Variables

I_{ptk} amount of product p stored over period t in scenario k

$Eprof$ expected operating profit

S_{ptk} amount of product p which is sold over period t in scenario k

T_{ptk} production time for product p at time period t in scenario k

T^{tot}_{tk} total production time over period t in scenario k

W_{ptk} amount of product p wasted over period t in scenario k

Δ_{ptk} amount of product p which is late over period t in scenario k

Integer Variables

B_{ptk} amount of product produced over period t in scenario k

Chapter 5

Medium Term Planning of Biopharmaceutical Manufacture using Chance Constrained Programming

5.1. Introduction

In the previous chapter, a two-stage programming approach for medium term planning of biopharmaceutical manufacture was presented using a mathematical programming formulation which determines the optimal production plans for a biopharmaceutical facility given uncertain fermentation titres. The overall problem was formulated as a two-stage MILP model based on discrete scenarios and an iterative algorithm was developed for its efficient solution.

The two-stage programming approach was compared to the deterministic model which demonstrated the value of decision-making under uncertainty in production planning of biopharmaceutical manufacture. The two-stage programming approach was also compared with the full space multiscenario model and a rolling horizon

algorithm where it was able to match or improve on both approaches in each of the example problems considered. The iterative algorithm presented was able to reduce considerably the computational burden associated with two-stage programming approaches. However, there are more ideal approaches for planning under uncertainty which can provide an alternative to multiscenario type representations and their associated computational burden.

In this chapter an alternative optimisation-based framework for medium term planning of biopharmaceutical manufacture given uncertain fermentation titres will be presented. This optimisation framework is also based on the deterministic medium term planning model presented earlier (Section 3.2) and leverages the concepts of chance constrained programming to represent the uncertain conditions. A compact mathematical formulation for medium term planning under uncertainty is presented and compared with the results from the deterministic formulation as well as the two-stage programming approach (CON/IMP) presented in the previous chapter (Sections 4.2 & 4.3). The results from four illustrative examples are presented.

5.2. Problem Description

As was discussed in Chapter 4, when tackling optimisation problems under uncertainty, parameters assumed to be uncertain are often represented by discrete outcomes using a multiscenario stochastic (two-stage) programming approach. Using a multiscenario approach and assuming between 3 and 10 products were to be produced, and with three possible outcomes for uncertain parameter r_p, resulted in between 27 and 59,049 possible scenarios (product/outcome combinations). Given that each scenario must be explicitly incorporated in the objective function, this exponential growth means that for larger examples solving the full space multiscenario model becomes computationally intractable. Practically the approach often adopted is to solve problems suboptimally by specially developed solution procedures such as that presented in Section (4.3).

Chance constrained programming (CCP) provides an alternative approach which avoids the multiscenario representation. Further discussion on the CCP methodology and the derivation of the problem formulation follows in the next section.

5.3. Mathematical Formulation

The formulation presented here is based on the deterministic medium term planning problem presented in Section 3.2, however again here the focus is shifted to tackling the impact of uncertainty. The deterministic formulation will first be presented and will be followed by the stochastic formulation.

5.3.1. Deterministic Formulation

The multiperiod MILP model composed of an objective function and constraints is formulated for the representation and solution of the biopharmaceutical production planning problem as shown below.

5.3.1.1. Production Constraints

Constraint (1) represents biopharmaceutical production. The number of batches produced, B_{pt}, an integer variable, is calculated through production rate, r_p, which is combined with production lead time, α_p. This lead time allows for the duration of the first batch of a campaign plus the set-up and cleaning time before the first batch is started. Production time, T_{pt}, shows the duration of manufacture of each product p within each time period t. The logical incorporation of lead time is enforced by a binary variable Z_{pt}. If a product p is selected for manufacture at time t a lead time, α_p, will only be included in that campaign duration to account for the setup and cleaning if Z_{pt} is equal to 1 (denoting the start of a new campaign).

$$B_{pt} = Z_{pt} + r_p (T_{pt} - \alpha_p Z_{pt}) \qquad \forall p,t \qquad (1)$$

Binary variable Y_{pt}, is introduced to denote whether or not a product p is manufactured at time t. In order to enforce the correct activation of binary variable Z_{pt}, constraint (2) is introduced. It enforces that Z_{pt} will only be activated if product p is not manufactured in the previous time period t-1, i.e. it is the start of a new campaign.

$$Z_{pt} \geq Y_{pt} - Y_{p,t-1} \qquad \forall p,t \qquad (2)$$

In order for the production constraints to capture accurately the campaign changeover considerations, constraint (3) is introduced to ensure that at most one product p undergoes manufacturing at any given time period t.

$$\sum_{p} Y_{pt} \leq 1 \qquad \forall t \qquad (3)$$

5.3.1.2. Timing Constraints

In some cases, manufacturers enforce minimum and/or maximum campaign lengths in order to maximise efficiency or to allow for relevant maintenance/slack. Constraints (4) and (5) represent the appropriate minimum and maximum production time constraints, where T_p^{min} is the minimum campaign duration, T_p^{max} is the maximum campaign duration and H_t is the size of the time horizon. These constraints are only active if Y_{pt} is equal to 1, otherwise the production times are forced to 0.

$$T_p^{\min} Y_{pt} \leq T_{pt} \qquad \forall p,t \qquad (4)$$

$$T_{pt} \leq \min\left\{T_p^{\max}, H_t\right\} Y_{pt} \qquad \forall p,t \qquad (5)$$

5.3.1.3. Storage Constraints

The following constraint enforces an inventory balance for production and forces production to meet demand. In constraint (6) the amount of product p stored at the end of the time period, I_{pt}, is equal to the amount stored at the previous time period, $I_{p,t-1}$, plus the net amount produced during the current time period, B_{pt}, less the amount sold, S_{pt}, and the amount of product wasted, W_{pt} in the current time period.

$$I_{pt} = I_{p,t-1} + B_{pt} - S_{pt} - W_{pt} \qquad \forall p,t \qquad (6)$$

Constraint (7) enforces that the amount of product p stored over period t cannot be negative and should not exceed the maximum available product storage capacity, C_p.

$$0 \le I_{pt} \le C_p \qquad \forall p,t \qquad (7)$$

In constraint (8) stored product is constrained by limited product lifetimes, whereby any product stored during time period t cannot be sold after the next ζ_p time periods.

$$I_{pt} \le \sum_{\theta=t+1}^{t+\zeta_p} S_{p\theta} \qquad \forall p,t \qquad (8)$$

5.3.1.4. Backlog Constraints

To ensure that late batches are eventually produced a penalty is incurred for every time period t that a given batch of product p is late. For a given product p at time t the number of late batches, Δ_{pt} is equal to the number of undelivered batches from the previous time period t-1, $\Delta_{p,t-1}$ plus demand at time t, D_{pt} less the sales at time t, S_{pt}. Late penalties are avoided by the penalty's minimisation in the objective function.

$$\Delta_{pt} = \Delta_{pt-1} + D_{pt} - S_{pt} \qquad \forall p,t \qquad (9)$$

5.3.1.5. Objective Function

The strategic objective in this formulation is to maximise operating profit. This is represented by an objective function which is considered to be the difference between "total sales" with each batch sold at a price v_p, and "total operating costs" which include the batch manufacturing cost at η_p per batch, changeover cost at ψ_p per batch, storage cost at ρ_p per batch and late delivery penalties of δ_p per batch. All costs and prices are in relative monetary units (rmu).

$$\text{Prof} = \sum_p \sum_t (v_p S_{pt} - \eta_p B_{pt} - \psi_p Z_{pt} - \rho_p I_{pt} - \delta_p \Delta_{pt}) \qquad (10)$$

The complete deterministic formulation [DET] is a MILP model comprising constraints (1– 10). The following section derives the stochastic formulation.

5.3.2. Stochastic Formulation

In this particular formulation the fermentation titres are considered to be uncertain as discussed in Section 5.1. They are captured as fluctuations in the production rate, r_p, through the proposed CCP model.

The CCP approach aims to satisfy constraints with a specified probability or confidence level and provide the optimal solution at that confidence level (Charnes and Cooper, 1959). This requires the decision maker to express a risk tolerance, in terms of a permissible probability of constraint violation which can be represented by a corresponding inverse cumulative distribution factor known as the critical K value, $\Phi^{-1}(K)$. For the efficient solution of the problem formulation, the deterministic equivalent formulation must be derived. Deterministic equivalent formulations of chance constraints can be derived using traditional probability theory concepts (Taha, 2003). The case of uncertain production rates is now considered.

5.3.2.1. Uncertain Production Rates

Consider the previous production constraint (1) from section 5.2.1.1 shown below.

$$B_{pt} = Z_{pt} + r_p(T_{pt} - \alpha_p Z_{pt}) \qquad \forall p,t \qquad (1)$$

where r_p is an uncertain parameter with mean $\mu(r_p)$ and standard deviation $\sigma(r_p)$.

In order to set up the chance constraint, it must first be converted into an inequality. In a planning problem where production is maximised the logical replacement of the "equality" sign =, is the "less than or equal to" sign ≤, as production B_{pt} is maximised in order to satisfy demand.

$$B_{pt} \leq Z_{pt} + r_p(T_{pt} - \alpha_p Z_{pt}) \qquad (11)$$

Formulating this as a chance constraint:

$$\Pr\left(B_{pt} \le Z_{pt} + r_p(T_{pt} - \alpha_p Z_{pt})\right) \ge \mathrm{A} \tag{12}$$

where A, is a minimum prespecified probability that constraint (12) will hold true. The feasibility of constraint (12) is a "good" event as this ensures the correct number of batches are produced, hence A should be large (> 50%).

Rearranging constraint (12):

$$\Pr\left(B_{pt} - Z_{pt} \le r_p(T_{pt} - \alpha_p Z_{pt})\right) \ge \mathrm{A} \tag{13}$$

Subtracting the mean of uncertain parameter $\mu(r_p(T_{pt} - \alpha_p Z_{pt}))$ and dividing both sides of constraint (13) by the standard deviation $\sigma(r_p(T_{pt} - \alpha_p Z_{pt}))$.

$$\Pr\left(\frac{B_{pt} - Z_{pt} - \mu\left(r_p(T_{pt} - \alpha_p Z_{pt})\right)}{\sigma\left(r_p(T_{pt} - \alpha_p Z_{pt})\right)} \le \frac{r_p(T_{pt} - \alpha_p Z_{pt}) - \mu\left(r_p(T_{pt} - \alpha_p Z_{pt})\right)}{\sigma\left(r_p(T_{pt} - \alpha_p Z_{pt})\right)}\right) \ge \mathrm{A} \tag{14}$$

Call the right-hand side of the inequality $\frac{r_p(T_{pt} - \alpha_p Z_{pt}) - \mu\left(r_p(T_{pt} - \alpha_p Z_{pt})\right)}{\sigma\left(r_p(T_{pt} - \alpha_p Z_{pt})\right)}$, h.

$$\Pr\left(\frac{B_{pt} - Z_{pt} - \mu\left(r_p(T_{pt} - \alpha_p Z_{pt})\right)}{\sigma\left(r_p(T_{pt} - \alpha_p Z_{pt})\right)} \le h\right) \ge \mathrm{A} \tag{15}$$

Rearranging constraint (15):

$$1 - \Pr\left(h \le \frac{B_{pt} - Z_{pt} - \mu\left(r_p(T_{pt} - \alpha_p Z_{pt})\right)}{\sigma\left(r_p(T_{pt} - \alpha_p Z_{pt})\right)}\right) \ge \mathrm{A} \tag{16}$$

$$\Pr\left(h \le \frac{B_{pt} - Z_{pt} - \mu\left(r_p(T_{pt} - \alpha_p Z_{pt})\right)}{\sigma\left(r_p(T_{pt} - \alpha_p Z_{pt})\right)}\right) \le 1 - \mathrm{A} \tag{17}$$

Assuming the left-hand side of the inequality h, is a stable normally distributed variable with a mean of 0 and a variance of 1, the chance constraint (17) can be replaced by constraint (18), where Φ, is the standardised normal cumulative distribution function.

$$\Phi\left(\frac{B_{pt} - Z_{pt} - \mu\left(r_p(T_{pt} - \alpha_p Z_{pt})\right)}{\sigma\left(r_p(T_{pt} - \alpha_p Z_{pt})\right)}\right) \leq 1 - \mathrm{A} \tag{18}$$

Applying the inverse of the standardised normal cumulative distribution function to constraint (18):

$$\frac{B_{pt} - Z_{pt} - \mu\left(r_p(T_{pt} - \alpha_p Z_{pt})\right)}{\sigma\left(r_p(T_{pt} - \alpha_p Z_{pt})\right)} \leq \Phi^{-1}(1 - \mathrm{A}) \tag{19}$$

Rearranging constraint (19), we get:

$$B_{pt} \leq Z_{pt} + \left(\mu(r_p) + \Phi^{-1}(1 - \mathrm{A}).\sigma(r_p)\right)(T_{pt} - \alpha_p Z_{pt}) \tag{20}$$

Finally, it follows naturally that $\Phi^{-1}(1-\mathrm{A})$ is equal to $-\Phi^{-1}(\mathrm{A})$. Hence in the chance constrained programming formulation, constraint (21) below becomes the new production constraint replacing constraint (1):

$$B_{pt} \leq Z_{pt} + \left(\mu(r_p) - \Phi^{-1}(A).\sigma(r_p)\right)(T_{pt} - \alpha_p Z_{pt}) \tag{21}$$

The complete deterministic equivalent formulation [CCP] becomes a MILP model comprising constraints (2 – 10) & (21). The following section illustrates the use of the proposed formulation through some illustrative examples.

5.4. Illustrative Examples

Four examples are solved to illustrate the applicability of the proposed CCP approach. All examples are solved assuming the production rate, r_p is uncertain. For sensitivity purposes the examples are solved for two different variabilities, +/- 10% and +/- 20% variability in the production rate, r_p. The results achieved using the CCP approach are compared with those achieved by the deterministic model (DET) presented in Section 5.2.1 which assumes mean values for the uncertain parameter r_p,

and the two-stage programming approach (CON/IMP) presented in Sections 4.2 and 4.3.

Similarly to Chapter 4, Monte Carlo (MC) simulation was used to conduct a stochastic analysis for each of the examples solved in order to better quantify the impact of variability on the deterministic schedules, as well as for the validation of the quality of solution schedules and thus the realistic expected performance. Subsequent to the solution of each optimisation model the resulting scheduling decision variables Y_{pt} and Z_{pt} are fixed and a MC analysis is conducted for uncertain parameter r_p and the expected profit (MCPROF) is computed. The convergence criteria for the MC simulation is a standard error of the mean of 1%.

The data used in the chance constrained programming approach assumes a mean of r_p and a standard deviation of $unc*r_p$ where *unc* is a fractional value which signifies a symmetrical deviation representing the variability from the mean. For the two-stage multiscenario model three discrete outcomes are assumed and their equivalent probabilities are derived by truncation of a standard normal distribution with mean r_p and standard deviation $unc*r_p$, by +/- 1 σ and the results are shown in Figure 5.1.

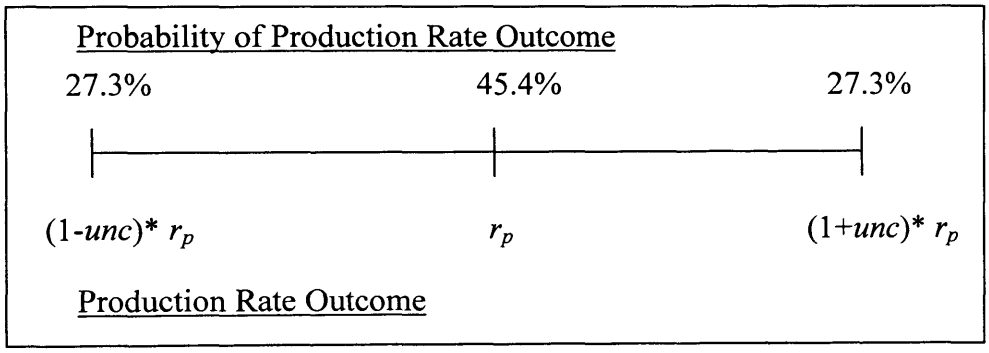

Figure 5.1: Equivalent discrete probability distribution of production rate r_p, where unc is the variability in r_p.

The confidence level of chance constraint feasibility for A is assumed to be 90% which in standard normal distribution tables (Ott and Mendenhall, 1990) corresponds to a critical K value ($\Phi^{-1}(K)$) of 1.282. All problems were implemented in GAMS

(Brooke *et al.*, 1998) using the CPLEX MILP solver, solving all problems to optimality. All runs were performed on a 1.8 GHz Pentium 4 PC with 512 MB RAM.

5.4.1. Example Problem Data

The sizes of each of the four examples tackled are shown below:

- Example 1: *three* products, *nine* time periods (1.5 year production time horizon).
- Example 2: five products, *ten* time periods (1.7 year production time horizon).
- Example 3: *seven* products, *twelve* time periods (2 year production time horizon).
- Example 4: *ten* products, *eighteen* time periods (3 year production time horizon).

The data associated with Examples 1 to 4 are presented below.

- A multiproduct facility producing p mammalian-cell-derived products is assumed, with one, two or three product orders for each product.
- A production horizon between 1.5 and 3 years long, split into t time periods each two months long, i.e. the production time horizon H_t, is 61 days long.
- The due date and demand profiles are shown in Tables 5.1 to 5.4. Orders were assumed to be due at the end of each two month time period t. Early delivery is assumed to be infeasible and late deliveries are penalised for each late period.
- Production rates, lead times and related parameters used in Examples 1 to 4 are shown in Table 5.5. Example 1 is assumed to include, P1-P3, Example 2, P1-P5, Example 3, P1-P7, and Example 4, P1-P10.
- All lead times α_p are in "days" and are each assumed to include seven days of product changeover related cleaning time.

*Table 5.1: Demand profile for Example 1**

Product	*Time Period*								
	i	2	3	4	5	6	7	8	9
P1			3			2			
P2				3				5	
P3		2							5

*Note: All demands are in number of batches

*Table 5.2: Demand profile for Example 2**

Product	*Time Period*									
	1	2	3	4	5	6	7	8	9	10
P1					2					
P2										3
P3			2			2		2		
P4		2		3					2	
P5						3				

*Note: All demands are in number of batches

*Table 5.3: Demand profile for Example 3**

Product	*Time Period*											
	1	2	3	4	5	6	7	8	9	10	11	12
P1					2				2			
P2												4
P3								2				
P4		2		3								
P5										2		
P6						3				3		
P7				3								

*Note: All demands are in number of batches

*Table 5.4: Demand profile for Example 4**

Product	*Time Period*																	
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
P1														4				
P2						3												
P3										2								
P4			2			3												
P5								2								3		
P6											3		4					
P7				3														
P8																3		
P9	2																	
P10																		3

*Note: All demands are in number of batches

Table 5.5: Parameters used in Examples 1-4, 1: P1-P3, 2: P1-P5, 3: P1-P7 & 4: P1-P10

Product	*Parameter data*			*Sales price and Costs*			
	r_p (batches/ day)	α_p (days)	T^{min}_p (days)	Price/Cost	Symbol	Unit	Value
P1	0.05	30	20	Product lifetime,	ζ_p	time periods	3
P2	0.0909	28	11				
				Storage	C_p	batch/day	6
P3	0.0625	32	16	Capacity,			
P4	0.05	30	20	Sales price,	υ_p	rmu/batch	10
P5	0.08	31	12.5				
				Manufacturing	η_p	rmu/batch	4
P6	0.05	30	20	cost			
P7	0.0909	28	11	Storage cost	ρ_p	rmu/batch	0.2
P8	0.08	31	12.5				
				Late penalty	δ_p	rmu/batch	4
P9	0.05	30	20				
P10	0.0909	28	11	Changeover cost	ψ_p	rmu/batch	2

5.4.2. Example Problem Results

All four examples were solved using DET, CCP and CON/IMP at 10% and 20% production rate r_p variability and the computational results are shown in Table 5.6, while Figure 5.2 shows graphical representations of the achieved expected profits (MCPROF). A discussion on the impact of uncertainty, solution quality and solution times follows below.

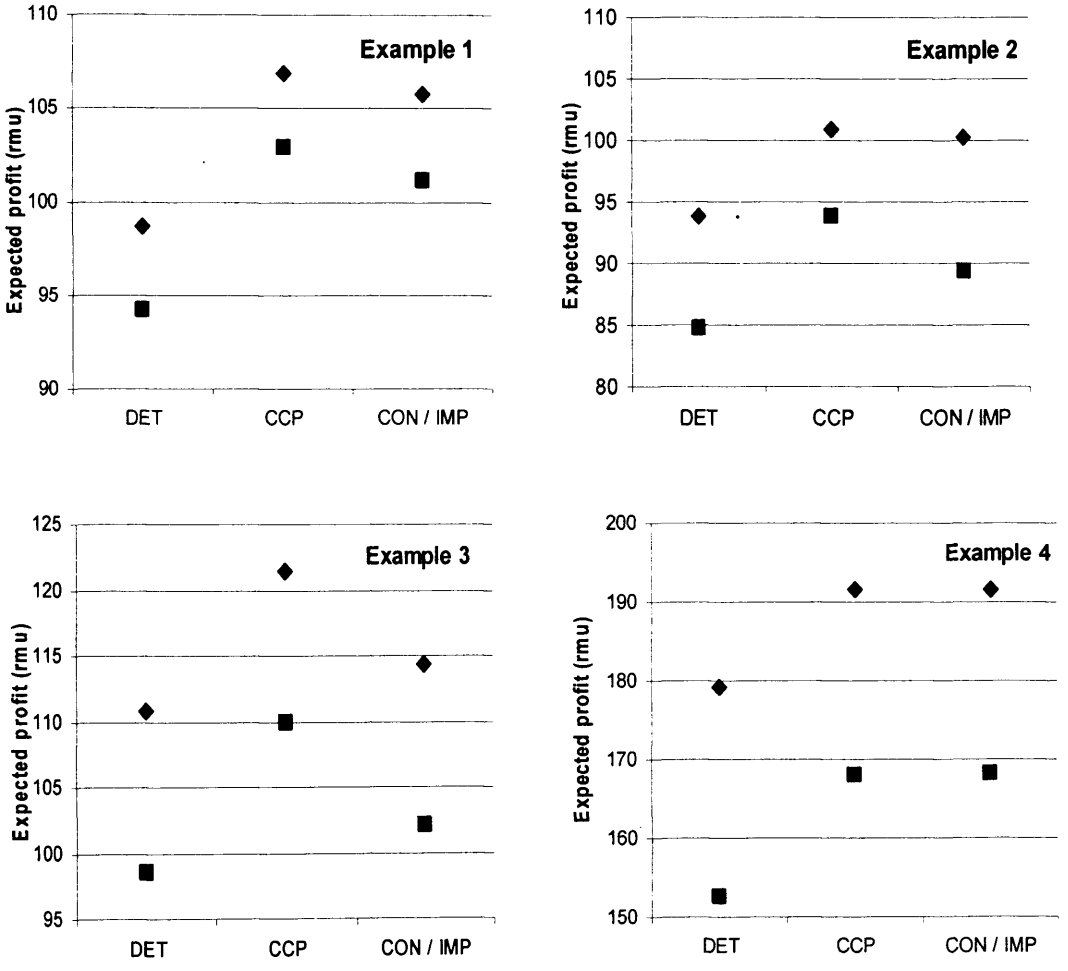

Figure 5.2: Graphical representations of achieved expected profits (MCPROF) for Examples 1, 2, 3 and 4 using DET (deterministic model), CCP (Chance constrained programming approach) and CON/IMP (Iterative construction/improvement algorithm), where ♦ represents 10% variability and ■ represents 20% variability.

As was seen in Chapter 4 (which included Examples 1, 2 and 4 from this chapter) there is a considerable negative impact on operating profits when not accounting for uncertainty. The CCP approach is able to make considerable improvements on the deterministic model in each of the four examples. The achieved percentage improvement on the deterministic model by the CCP and the CON/IMP algorithm can be seen in Table 5.7.

Table 5.6: Computational results for Examples 1-4.*

Computational Results		**Optimisation (CPU: in seconds)**				**Monte-Carlo Simulation**	
Indicator		**OBJ**		**CPU**		**MCPROF**	
% variability for r_p		**10**	**20**	**10**	**20**	**10**	**20**
	DET	108.5	108.5	1	1	**98.7**	**94.2**
Example 1	**CCP**	106.7	96.7	1	1	**106.9**	**102.9**
	CON/IMP	105.8	105.8	19	14	**105.8**	**101.1**
	DET	109.5	109.5	1	1	**93.9**	**84.8**
Example 2	**CCP**	102.9	76.9	1	3	**100.9**	**93.8**
	CON/IMP	104.9	100.4	26	24	**100.3**	**89.4**
	DET	135.7	135.7	1.3	1.3	**110.8**	**98.5**
Example 3	**CCP**	114.3	114.3	1	1	**121.4**	**109.9**
	CON/IMP	135.8	131.2	18	17	**114.4**	**102.1**
	DET	195.6	195.6	2.9	3.0	**179.2**	**152.6**
Example 4	**CCP**	193.6	171.8	4.3	18.8	**191.6**	**168.0**
	CON/IMP	195	195	32	31	**191.7**	**168.2**

*Note: Optimisation objective function (OBJ), Solution time in seconds (CPU) and Monte-Carlo simulation objective function (MCPROF); for results from DET (Deterministic model), CCP (Chance constrained programming approach) and CON/IMP (Iterative construction/improvement algorithm).

The CCP approach is found to make considerable improvements over the deterministic model as can be seen graphically in Figure 5.2 or numerically in Table 5.7. Across all examples the CCP approach makes improvements of between 6.9% and 10.6%. In all examples the higher variability scenario of 20% results in greater improvements in solution quality and hence higher potential monetary savings. The consistency and quality of the improvements can be attributed to improved scheduling decisions and hence more timely satisfaction of demands. Timely demand

satisfaction reduces the lateness penalties which have the greatest impact on the objective function. In the case of CCP a combination of improved scheduling decisions and improved capacity utilisation leads to more timely demand satisfaction and lower productions costs, leading to an even greater improvement in profits.

Table 5.7: Percentage improvement in expected profit over the deterministic model solution for Examples 1-4.*

% variability for r_p		10	20
Example 1	**CCP**	8.3	9.2
	CON/IMP	[illegible]	[illegible]
Example 2	**CCP**	7.5	10.6
	CON/IMP	6.8	5.4
Example 3	**CCP**	9.6	11.6
	CON/IMP	3.2	3.7
Example 4	**CCP**	6.9	10.1
	CON/IMP	7.0	10.2

CCP (Chance constrained programming approach) and CON/IMP (Iterative construction/improvement algorithm).

The CCP approach consistently improves on or matches the CON/IMP algorithm. CCP achieves up to 300% relative improvement over the solution quality achieved by the CON/IMP algorithm. However, the value of the CCP approach is not only in the improved performance of solution quality under the impact of uncertainty but also in the negligible increase in CPU time that is traditionally a cumbersome feature of typical multiscenario, stochastic programming models. When compared directly to the CON/IMP algorithm from a solution time perspective, CCP generally outperforms the algorithm, given that the CCP approach does not employ the scenario index k and hence generates a model size almost identical to that generated by the deterministic approach. In the largest example, Example 4, the number of scenarios that would be generated by a full-scale multiscenario representation assuming three discrete outcomes would be greater than $5.9 \times 10^{\wedge 4}$ scenarios, which would be difficult to solve in any reasonable timescale with conventional computer hardware. The computational requirements in all examples and variability scenarios are reasonable. The CPU times achieved by the CCP approach are generally of a

similar order of magnitude as those achieved by the deterministic model, with the longest CPU time for CCP being less than 19 seconds. Considering the size of the largest example solved, this demonstrates the exceptional computational efficiency of the proposed CCP approach.

5.5. Conclusions

In this chapter, a mathematical optimisation-based framework for medium term biopharmaceutical manufacturing planning under uncertainty has been presented, and tested on four illustrative examples of different size and at different variabilities. The problems were all solved using a deterministic model (DET), a two-stage programming model accompanied by an iterative construction algorithm (CON/IMP) and the proposed chance constrained programming approach (CCP). The results of the MC analysis showed that CCP consistently improved on the results of DET in terms of profitability. While when compared with the CON/IMP algorithm the CCP approach was able to match or improve on it in terms of both solution quality and computational time.

5.6. Nomenclature

Indices

p	product
t, θ	time periods

Parameters

C_p	storage capacity of product p, batches
D_{pt}	demand of product p at time period t
r_p	production rate of product p, batches per unit time

H_t available production time horizon over time period t

T^{max}_p maximum production time for product p

T^{min}_p minimum production time for product p

α_p lead time for production of first batch of product p

ζ_p life time of product p, number of time periods t

υ_p unit sales price for each batch of product p

η_p unit cost for each batch produced of product p

ψ_p unit cost for each new campaign of product p

δ_p unit cost charged as penalty for each late batch of product p

ρ_p unit cost for each stored batch of product p

$\mu(r_p)$ the mean value of production rate and is equivalent to r_p

$\sigma(r_p)$ the standard deviation of production rate r_p

Φ^{-1} inverse of the standardised normal cumulative distribution function

Binary Variables

Y_{pt} 1 if product p is produced over period t; 0 otherwise

Z_{pt} 1 if a new campaign of product p is started in period t; 0 otherwise

Continuous Variables

I_{pt} amount of product p stored over period t

$Prof$ operating profit

S_{pt} amount of product p which is sold over period t

T_{pt} production time for product p at time period t

T^{tot}_t total production time over period t

W_{pt} amount of product p wasted over period t

Δ_{pt} amount of product p which is late over period t

Integer Variables

B_{pt} amount of product produced over period t

Chapter 6

Multiobjective Long Term Planning of Biopharmaceutical Manufacturing Facilities

6.1. Introduction

In the previous Chapters (3-5), approaches for medium term planning of biopharmaceutical manufacture were presented, whereby the focus was production planning of a single biopharmaceutical facility. Both deterministic and stochastic approaches were developed. However the models did not account for longer term strategic objectives, where multiple facilities are often considered simultaneously. As an increasing number of large-scale biopharmaceutical companies have a portfolio of commercial products on the market as well as a pipeline of candidates under clinical evaluation, developing a comprehensive manufacturing strategy to meet anticipated demands for both clinical trial and market material requires careful capacity planning. Consequently, more effective methods are required to manage and align production across several multiproduct facilities, including third party organisations, so as to ensure the availability of sufficient capacity. However, determining capacity needs for biopharmaceutical production is often a difficult process requiring

predictions of product doses, market forecasts, production rates (titres, yields) and clinical/technical success rates.

Hence in this chapter we consider the issue of long term production planning in the biopharmaceutical industry. The work in this chapter is motivated by an industrial case study based upon a large-scale biopharmaceutical manufacturer who wishes to improve their long term planning decisions and to explore the impact of different strategic decision making policies. We present an MILP formulation for the long term production planning of biopharmaceutical manufacture and later extend it via a goal programming formulation to account for multiple objectives. The industrial case study is solved and analysed to demonstrate the applicability of the model and highlight some of the key challenges within strategic decision-making in the biopharmaceutical industry.

6.2. Problem Features

The biopharmaceutical supply chain is comprised of two main stages much like that of the pharmaceutical industry, namely primary (or bulk) manufacture which involves the production of the active ingredient and secondary manufacture which involves formulation and packaging. The focus of this chapter is on manufacturing production planning across a network of facilities to satisfy bulk product demands. The key features of the problem particularly those highlighted in this work are discussed below.

6.2.1. Plant Capacity

For a good estimate of a manufacturer's capacity availability and requirements the key features of biopharmaceutical manufacturing must be captured. These features include the long production lead times encountered and the level of time granularity used for the planning horizon. This should be sufficiently fine to mimic the "campaign" style manufacture often adopted in the biopharmaceutical industry, which is typically 2 to 3 months per campaign. A manufacturer often uses owned

facilities and/or contractors with differing manufacturing rates, yields, production capabilities and availabilities. These need to be represented explicitly and are often based on forecasted yields and product success rates.

6.2.2. Product Storage

Product instability and hence shelflife is an important and often costly feature of biopharmaceuticals. Products are often frozen via specialised storage methods such as cryopreservation offering manufacturers increased flexibility for scheduling and planning (Wilkins *et al.*, 2001). Shelflife is of great significance to the effective management of inventory given that some products are required in very small doses but produced in larger bulk orders (economies of scale) requiring products to be held to meet future order dates.

6.2.3. Product Pricing, Demand and Backlog

Product pricing is established through research with physicians, patients, payers, and advocacy groups and are also impacted by a drug's uniqueness, competitive pricing strategies and socio-political factors (Snow *et al.*, 2005). Meeting product demand in the biopharmaceutical industry is a highly sensitive issue due to the high value of the products involved. Mallik (2002) estimates that the lack of manufacturing capacity for Immunex's highly successful arthritis drug Enbrel cost the company more than $200 million in lost revenue in 2001, while Shah (2004) notes that Eli Lilly's 20% drop in net profits coincided with Prozac coming off patent. Hence companies must therefore strive to capture every day of revenue generation by ensuring an adequate supply of product. Penalties should ensure that late deliveries are made as soon as possible. If demands are unmet by their order dates, backlog of demand should be captured to ensure that demands are met as soon as possible. However, typically the importance of satisfying backlogged orders decays with time as new orders take precedence.

6.2.4. Strategic and Operational Objectives

There are many possible strategic and operational objectives for a biopharmaceutical manufacturer as there are many different stakeholders and both internal and external pressures. Hence the strategic decision making policies a manufacturer adopts are likely to have varying consequences on different performance measures. Even though the livelihood of a business is inevitably governed through the maximisation of its shareholder value, there are many constraints to meeting this long term goal. Possible objectives include maximising profit, maximising sales, maximising customer service level, minimising costs, and minimising risk to name but a few. Other objectives are to meet targets such as satisfying fixed cost or capacity utilisation targets and hence might not be expressed as outright maximisation or minimisation problems.

We first consider a common single objective problem where operating profits are maximised, followed by a multi-objective problem where the three objectives considered are: operating costs, customer service level and capacity utilisation of owned facilities. Operating cost targets are usually dictated either by budget constraints or a drive to be more cost-effective. Customer service levels may also be set as strategic targets to ensure that customer demand is met on time. Another important issue from an operational perspective is plant capacity utilisation; Mallik (2002) estimated that in a typical new mammalian cell-culture facility revenues would be boosted by $380M by a 25% increase in plant utilisation. Manufacturers often have strategic capacity utilisation targets for their owned facilities (adjusted for market uncertainty and manufacturing risks), in order to ensure high utilisation of their facilities and hence minimise facility carrying costs (idle facility costs) and the need for outsourced capacity. Another feature incorporated here is manufacturing risk, whereby it is defined as the risk of a manufacturing facility outage due to unforeseen circumstances such as a contractor manufacturer dispute or natural disaster.

6.3. Problem Statement

The problem of long term planning of biopharmaceutical manufacture may be stated as follows.

Given:

- A set of facilities.
- A set of products.
- A production time horizon.
- Production rates, yields and lead times.
- Product lifetimes and storage capacities.
- Product demands and sales prices.
- Backlog decay factor.
- Manufacturing, changeover, storage costs and late delivery penalties.
- Minimum and maximum campaign durations.
- Goal Target values and weights for: Cost, service level and capacity utilisation.

Determine:

- Campaign durations and sequence of campaigns.
- Production quantities along with inventory profiles.
- Product sales and late deliveries profile.
- Achieved goal levels vs. aspired goal targets.

So as to

- Maximise manufacturing profits (Single objective problem).
- Minimise the total adverse deviations from the selected goal targets (Multiobjective problem).

6.4. Mathematical Formulation

The formulation presented here is based on the work presented earlier (Section 3.2) where we tackled a deterministic medium term planning problem. Here the focus is shifted to longer term planning allowing for multiple facilities. A single objective formulation is presented first, before moving to a goal programming extension to allow for multiple objectives.

6.4.1. Long Term Planning Formulation

An index i denoting facility is introduced to the formulation presented earlier (Section 3.2) to allow for multiple facilities. This manufacturing representation is more akin to a multisuite configuration than that of a multisite one with geographically distinct sites as features such as transportation costs and differing taxation regions are not considered. Subsets are introduced for facility manufacturing capability, PI_i the set of products produced by facility i and for facility availability, product manufacturing capability, IP_p the set of facilities that can produce product p TI_i the set of time periods in which facility i is available for use.

6.4.1.1. Production Constraints

Constraint (1) represents biopharmaceutical production. The number of batches produced in facility i of product p at time period t, B_{ipt}, an integer variable, is represented by a continuous production rate, r_{ip}, which is combined with production lead time, α_{ip}. This allows for the duration of the first batch of a campaign plus the set-up and cleaning time before the first batch is started. Production time, T_{ipt}, shows the duration of manufacture in facility i of product p at time period t. Incorporation

of lead time is enforced by a binary variable Z_{ipt}. If a facility i is selected to manufacture a product p at time t a lead time, α_{ip}, will only be included in that campaign duration to account for the setup and cleaning if Z_{ipt} is equal to 1 (denoting the start of a new upstream/downstream campaign). Constraint (2) is introduced for the conversion of the integer number of batches produced, B_{ipt}, into kilograms, K_{ipt}, via a yield conversion factor, yd_{ip}, specific to every product p and facility i. (This differs for different facilities even for the same product as it allows for different batch sizes and product titres).

$$B_{ipt} = Z_{ipt} + r_{ip}(T_{ipt} - \alpha_{ip} Z_{ipt}) \qquad \forall i, p \in PI_i, t \in TI_i \qquad (1)$$

$$K_{ipt} = B_{ipt}\, yd_{ip} \qquad \forall i, p \in PI_i, t \in TI_i \qquad (2)$$

Binary variable Y_{ipt}, is introduced to denote whether or not a facility i is used to manufacture a product p at time t. In order to enforce the relevant production lead times constraint (3) is introduced. It enforces that Z_{ipt} in constraint (1) will only be activated if product p is not manufactured at a facility i in the previous time period t-1, i.e. it is the start of a new campaign upstream.

$$Z_{ipt} \geq Y_{ipt} - Y_{ip,t-1} \qquad \forall i, p \in PI_i, t \in TI_i \qquad (3)$$

In order for the production constraints to capture the required campaign changeover considerations, constraint (4) ensures that at most one product p undergoes manufacturing in any given facility i at any given time period t.

$$\sum_{p \in PI_i} Y_{ipt} \leq 1 \qquad \forall i, t \in TI_i \qquad (4)$$

6.4.1.2. Timing Constraints

In some cases, manufacturers enforce minimum and/or maximum campaign lengths in order to maximise efficiency or to allow for relevant maintenance/slack. Constraints (5) and (6) represent the appropriate minimum and maximum production time constraints, where T_{ip}^{min} is the minimum campaign duration, T_{ip}^{max} is the

maximum campaign duration and H_t is the size of the time horizon. These constraints are only active if Y_{ipt} is equal to 1, otherwise the production times are forced to 0.

$$T_{ip}^{\min} Y_{ipt} \leq T_{ipt} \qquad \forall i, p \in PI_i, t \in TI_i \qquad (5)$$

$$T_{ipt} \leq \min\left\{T_{ip}^{\max}, H_t\right\} Y_{ipt} \qquad \forall i, p \in PI_i, t \in TI_i \qquad (6)$$

Constraint (7) shows the facility production time, Tf_{it}^{tot} for all products is equal to the summation of the individual production times for each product p.

$$Tf_{it}^{tot} = \sum_{p \in PI_i} T_{ipt} \qquad \forall i, t \in TI_i \qquad (7)$$

6.4.1.3. Storage Constraints

The following constraint enforces an inventory balance for production and forces total production to meet product demand. In constraint (8) the amount of product p stored at the end of the time period I_{pt}, is equal to the amount at the previous time period I_{pt-1}, plus the total number of batches produced during the time period for all products across all facilities i, B_{ipt}, less the amount sold, S_{pt}, and the amount of product wasted, W_{pt} in the current time period t.

$$I_{pt} = I_{p,t-1} + \sum_i K_{ipt} - S_{pt} - W_{pt} \qquad \forall p \in PI_i, t \in TI_i \qquad (8)$$

Constraint (9) enforces that the amount of product p stored over period t cannot be negative and should not exceed the maximum product storage capacity, C_p. While constraint (10) enforces that the sum of the total inventory held at any given time t cannot exceed the global storage capacity CP^{tot}.

$$0 \leq I_{pt} \leq C_p \qquad \forall p, t \qquad (9)$$

$$0 \leq \sum_p I_{pt} \leq CP^{tot} \qquad \forall t \qquad (10)$$

In constraint (11), the duration a product is stored for (shelf-life) is limited by product-lifetimes. It effectively ensures that final product is sold in less than ζ_p time periods from when it is first stored.

$$I_{pt} \leq \sum_{\theta=t+1}^{t+\zeta_p} S_{p\theta} \qquad \forall p,t \qquad (11)$$

6.4.1.4. Backlog Constraints

To ensure that late batches are eventually produced a penalty is incurred for every time period t that a given batch of product p is late. For a given product p at time t the number of late batches, Δ_{pt} is equal to the number of undelivered batches from the previous time period t-1 multiplied by a factor π_p which allows for the backlog to decay (due to the diminishing importance of the backlogged orders), $\pi_p \Delta_{p,t-1}$ plus demand at time t, D_{pt} less the sales at time t, S_{pt}. Late penalties are avoided by the penalty's minimisation in the objective function.

$$\Delta_{pt} = \pi_p \Delta_{pt-1} + D_{pt} - S_{pt} \qquad \forall p,t \qquad (12)$$

6.4.1.5. Risk Constraints

The risk of a facility outage due to an unforeseen circumstance such as a natural disaster or a dispute with a contract manufacturer or any other circumstance must be mitigated. A facility should be enforced to meet demands by producing a given product in at least two different facilities where possible. In some cases product demands may be too small or only one facility may be capable of producing a particular product. In such cases products to be constrained are included in a subset, *RS*, the set of products which should be manufactured in at least two different facilities.

A new set is introduced, TB_b the set of time periods in a time block b. This allows the specification of a time window in which to enforce products to be manufactured more than once. A new binary variable Y_{ipb}^{new} which is activated if a facility i is used to manufacture a product p within a time block b. Constraint (13) enforces any

product belonging to the set RS to be produced in at least two different facilities i within any time block b. Constraint (14) relates Y_{ipb}^{new} to binary variable Y_{ipt} while production time T_{ipt} is related through constraints (5) and (6).

$$\sum_{i \in IP_p} Y_{ipb}^{new} \geq 2 \qquad \forall p \in RS, b \qquad (13)$$

$$\sum_{t \in TB_b \cap TI_i} Y_{ipt} \geq Y_{ipb}^{new} \qquad \forall i \in IP_p, p \in RS, b \qquad (14)$$

6.4.1.6. Objective Function

The objective function "maximise profit" is represented here and is considered to be the difference between "total sales" with each batch sold at a price v_p, and "total operating costs" which include the batch manufacturing cost at η_p per batch, changeover cost at ψ_p per batch, storage cost at ρ_p per batch and late delivery penalties of δ_p per batch. All costs and prices are in relative monetary units (rmu).

[Model SINGLE]

Maximise

$$\text{Prof} = \sum_{p} \sum_{t \in TI_i} (v_p S_{pt} - \rho_p I_{pt} - \delta_p A_{pt} - \sum_{i IP_p} (\eta_{ip} B_{ipt} + \psi_{ip} Z_{ipt})) \qquad (15)$$

Subject to: constraints (1 – 14).

The complete formulation SINGLE encompassing equations (1 – 15) corresponds to a mixed-integer linear programming (MILP) model.

6.4.2. Goal Programming Formulation

Here we consider the case of multiple objectives. Many methodologies have been proposed for treating multiobjective optimisation problems (Miettinen, 1999). A general review of the application of multiobjective optimisation in chemical

engineering is presented by Bhaskar *et al.* (2000). A number of multiobjective optimisation methods have been applied to supply chain and strategic planning problems, including Life-Cycle Assessment (LCA) (ISO, 1997) which is a quantitative environmental performance tool, based around mass and energy balances but applied to a complete economic system rather than a single process. Azapagic and Clift (1999) applied LCA across supply chains to improve environmental performance, by generating Pareto fronts and trading off economic performance. The ε-constraint method (Haimes *et al.*, 1971) is based on the maximisation of one objective function while considering the other objectives as constraints bounded by some allowable levels εo. Then, the levels εo may be altered to generate the entire Pareto-optimal set. Sabri and Beamon (2000) presented a multiobjective supply chain optimisation model which employed the ε-constraint method for the simultaneous strategic and operational supply chain planning. Multiobjective decision analysis was adopted to allow the use of a performance measurement system that included cost, customer service levels, and flexibility (volume or delivery). The model incorporated production, delivery, and demand uncertainty, and aimed to provide a multiobjective performance vector for the entire supply chain network. Guillén *et al.* (2005) combined the ε-constraint method with a two stage programming model to tackle the problem of design and retrofit of a supply chain network consisting of several production plants, warehouses and markets, and the associated distribution systems. The authors considered profit, demand satisfaction and financial risk allowing for uncertainty in demand, and generated a Pareto set of solutions to aid the decision maker. Another commonly utilised approach in tackling multiobjective optimisation problems is goal-programming (Charnes and Cooper, 1961) which is a generalisation of linear programming to handle multiple, normally conflicting objective measures. Each of these measures is given a goal or target value to be achieved. Unwanted deviations from this set of target values are then minimised as an achievement function. Zhou *et al.* (2000) presented a multiobjective optimisation framework in which goal programming and the analytic hierarchy process, a multiobjective decision making method used to evaluate the priorities of goals and weights of deviation variables, were combined to tackle the issue of sustainability in supply chain optimisation and

scheduling of a petrochemical complex. Multiple objectives including social, economic, resources and environmental sustainability; some of which were conflicting, were considered.

Each of the multiobjective optimisation methods considered above is based on the conversion of a vector of objectives into a scalar objective. Given that optimisation of a multiobjective problem is a procedure looking for a compromise policy, the resulting Pareto-optimal or noninferior solution set consists of an infinite number of options. In order to be able to suggest a specific point within this set, some attempts have been made to compare the objectives between them, for example optimising a Nash-type function (Gjerdrum *et al.*, 2001), defining the objectives as fuzzy sets (Chen *et al.*, 2003) or adding the consideration of the decision-maker input in the problem formulation Rodera *et al.* (2002).

A goal programming approach has been adopted so as to demonstrate the trade-offs between selected objectives for the following reasons: 1) goal programming does not dramatically increase the problem complexity/size, 2) no specific conditions are required to achieve the solutions, and 3) goal-programming is simple, since it transforms the multiobjective problem into a single-objective optimisation problem. There are several types of goal programming formulations (lexicographic, minimax, weighted, extended & interval). Tamiz *et al.* (1995) noted that lexicographic and weighted goal programming represented 85% of goal programming applications in the literature. Lexicographic goal programming was found to be too computationally intensive given the size of the problem considered in this work. Hence, weighted goal programming (WGP) is the method presented, whereby the normalised unwanted deviations are assigned weights according to their relative importance to the decision-maker and minimised as an Archimedean sum (sum up to 1).

Here, three different goals, g, are considered: cost, service level (csl) and capacity utilisation (util). Three key variables are introduced to relate the goals and aid their attainment: the goal target for each goal g, GT_g, the goal level of each goal g, GL_g, and the goal difference/deviation for each goal g, $GD_{g,\,dev}$. The deviation *dev* can be positive, *pos*, or negative, *neg*, whereby both $GD_{g,\,pos}$, and $GD_{g,\,neg}$, are positive variables. The goal difference $GD_{g,\,dev}$ is equivalent to the absolute difference

(differential) between the aspired goal target GT_g, and the achieved goal level GL_g, for each goal, g.

6.4.2.1. Operating Costs

Constraint (16) shows the cost goal which is defined as the total operating costs for all facilities, whereby the goal level for cost, GL_{cost} is equal to the summation of the inventory, late delivery penalties, manufacturing costs, and changeover costs. This should be *minimised* to at least meet its aspired target level, GT_{cost}.

$$GL_{\text{cost}} = \sum_{p \in PI_i} \sum_{t \in TI_i} \left((\rho_p I_{pt} + \delta_p \Delta_{pt}) + \sum_i (\eta_{ip} B_{ipt} + \psi_{ip} Z_{ipt}) \right) \qquad (16)$$

6.4.2.2. Customer Service Level

Constraint (17) shows the customer service level (CSL) goal which is defined as the proportion of the demand which is met on the due date. This is a similar concept to OTIF (on time and in full) (Gjerdrum *et al.*, 2001). Constraint (18) shows the CSL goal level, which is given as a percentage for each time period t, $GLT_{csl,t}$ and is equal to the difference between the total sales minus any backlogged batches as a proportion of the total demand. A subset DT is introduced and represents the set of time periods in which product demands are due.

$$GLT_{csl,t} = 100 * \sum_p \frac{S_{pt} - \Delta_{p,t-1}}{D_{pt}} \qquad \forall t \in DT \qquad (17)$$

$$GL_{csl} = \frac{\sum_{t \in DT} GLT_{csl,t}}{card(DT)} \qquad (18)$$

6.4.2.3. Capacity Utilisation

Constraint (19) shows the capacity utilisation goal which is defined as the utilisation of available manufacturing time for each facility. Constraint (20) shows the capacity

utilisation goal level which is given as a percentage for each facility i, $GLI_{util,i}$ and is equal to the total manufacturing time for each facility, Tf_{it}^{tot}, divided by the total available manufacturing time for each facility, where A_i is a scalar denoting the proportion of the time horizon that facility i is available.

$$GLI_{util,i} = \frac{100 * \sum_{t} Tf_{it}^{tot}}{H_t card_t A_i} \qquad \forall i \qquad (19)$$

A subset OS is introduced and represents the set of facilities which are owned by the manufacturer and hence are required to meet strategic capacity utilisation targets. As shown in constraint (20) the goal level for capacity utilisation, GL_{util}, is equal to the average capacity utilisation over all owned facilities. This should be *minimised or maximised* to meet its aspired target level, GT_{util}, exactly.

$$GL_{util} = \frac{\sum_{i \in OS} GLI_{util,i}}{card(OS)} \qquad (20)$$

6.4.2.4. Normalisation Constraints

Constraint (21) and (22) represent normalisation constraints for the goals and the goal deviations respectively, whereby each goal is normalised to 100. Goal levels, GL_g and goal deviations, $GD_{g,dev}$ are multiplied by 100 and divided by the goal targets GT_g. Normalisation is often desirable for the unbiased optimisation of goals of different magnitudes, meaning that the optimisation bias is completely transferred to the decision maker via the specification of goal weights.

$$GL_g^{norm} = \frac{GL_g * 100}{GT_g} \qquad \forall g \qquad (21)$$

$$GD_{g,dev}^{norm} = \frac{GD_{g,dev} * 100}{GT_g} \qquad \forall g, dev \qquad (22)$$

Constraint (23) represents the goal balance, where the normalised goal level for each goal, plus the negative and positive goal differences for each goal are equal to 100.

$$GL_g^{norm} + GD_{g,neg}^{norm} - GD_{g,pos}^{norm} = 100 \qquad GD_{g,neg}^{norm} GD_{g,pos}^{norm} \geq 0, \forall g \qquad (23)$$

6.4.2.5. Objective Function

The objective function for the multiobjective optimisation problem (MULTI) is the minimisation of the weighted sum of the normalised deviations from all goal target values and is shown below, where $WT_{g,dev}$ is the weight of each goal deviation.

[Model MULTI]

Minimise

$$\text{Sumd} = \sum_g \sum_{dev} WT_{g,dev} GD_{g,dev}^{norm} \qquad (24)$$

Subject to: constraints (1-14 & 16-23).

The complete formulation MULTI encompassing equations (1-14 & 16-24) also corresponds to a mixed-integer linear programming (MILP) model. The applicability of the model will now be demonstrated via an industrial case-study.

6.5. Industrial Case-Study

As an example of an industrial application, a case study based on a real-life planning problem facing a large-scale biopharmaceutical manufacturer is presented. This represents a typical capacity management problem in the biopharmaceutical industry, whereby a manufacturer has a mix of owned and contract manufacturing facilities available to them and must decide how to best utilise this capacity. A number of studies are presented based on the industrial case data and an analysis is conducted with relevant insights drawn.

First the problem data is presented, followed by a demand analysis and a quantification of the impact of allowing for manufacturing risk through the activation of the risk constraint. A capacity analysis is then conducted in order to establish the manufacturer's capacity needs. Finally the multiobjective problem is presented, whereby different operating policies and cost target levels are investigated and discussed.

6.5.1. Problem Data

This problem presents a challenging long term planning problem in the biopharmaceutical industry, whereby a manufacturer needs to decide how to best utilise ten manufacturing facilities for the production of fifteen biopharmaceutical products, over a fifteen-year time horizon. The problem definition and associated data are given below:

- Ten manufacturing facilities (i1 – i10), of which i1, i4, i6 and i9 are owned facilities while the rest are CMO, producing fifteen biopharmaceutical products (p1-p15).

- A fifteen year time horizon is assumed from 2006 – 2020, with 60 time periods t each three months long, i.e. the production time horizon H_t, is 87 days long (discounting 5% for maintenance time).

- The due date and demand profiles are shown in Table 6.1. Orders are assumed to be due at the end year, i.e. every four time periods. Early delivery is assumed to be infeasible.

- Table 6.2 shows the facility capabilities. All facilities are assumed to be available throughout the time horizon, apart from facility 6 (i6) which is unavailable until, 2007 (t5), and facility 9 (i9) which is unavailable until 2016 (t41). Minimum and maximum campaign durations are assumed to be 0 and 87 respectively.

- Production rates, manufacturing yields and manufacturing costs are shown in tables 6.3, 6.4 and 6.5 respectively. All remaining parameters are shown in Table 6.6.

Table 6.1: Product demands for industrial case study

Year	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
p1	21	32	18	28	61	104	153	156	164	63	161	162	162	163	165
p2	6	5	4	4	4	3	3	3	3	3	3	3	2	2	2
p3	12	43	38	5	22	52	97	132	133	135	137	118	109	100	90
p4	583	628	655	687	758	921	989	941	993	649	621	573	521	468	421
p5	12	12	11	10	9	7	6	5	4	3	2	2	2	2	3
p6	211	200	245	246	257	266	284	274	226	180	166	151	137	123	110
p7	4	5	5	7	6	5	8	9	8	9	7	7	6	5	5
p8	5	5	5	7	6	5	8	9	8	9	7	7	6	5	5
p9	15	15	15	13	12	9	8	6	5	4	3	3	2	2	2
p10	72	99	104	102	111	120	130	139	188	120	106	93	81	69	58
p11	552	615	699	737	743	733	684	572	518	471	424	381	342	307	274
p12	5	5	5	7	6	5	8	9	8	9	7	7	6	5	5
p13	211	252	290	298	286	216	169	153	150	145	110	100	93	84	102
p14	2	2	4	3	3	3	16	11	13	16	16	16	16	17	17
p15	4	4	5	6	16	11	24	32	37	40	41	42	42	43	44

Note: All demands are in kilograms

Table 6.2: Facility capability for industrial case study

	p1	p2	p3	p4	p5	p6	p7	p8	p9	p10	p11	p12	p13	p14	p15
i1	Yes	Yes	No	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
i2	Yes	No	No	Yes	No	Yes	No	Yes	No	Yes	Yes	No	Yes	Yes	Yes
i3	No	No	No	No	No	No	No	No	No	No	No	No	Yes	No	No
i4	No	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No
i5	No	No	No	Yes	No	No	No	Yes	No	Yes	Yes	No	No	Yes	Yes
i6	No	No	No	Yes	No	No	No	Yes	No	Yes	Yes	No	No	Yes	Yes
i7	No	No	No	No	No	No	Yes	No	No	Yes	No	No	No	No	No
i8	No	No	Yes	No	Yes	No	No	No	No	No	No	No	No	No	No
i9	Yes	No	No	Yes	No	Yes	No	No	No	Yes	Yes	No	No	Yes	Yes
i10	Yes	Yes	No	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Note: i1, i4, i6 and i9 are owned facilities

Table 6.3: Production rates for industrial case study

	p1	p2	p3	p4	p5	p6	p7	p8	p9	p10	p11	p12	p13	p14	p15
i1	0.35	0.39	0	0.45	0	0.29	0	0.35	0.25	0.39	0.41	0.39	0	0.12	0.35
i2	0.6	0	0	0.61	0	0.6	0	0.6	0	0.43	0.56	0	0.6	0.6	0.6
i3	0	0	0	0	0	0	0	0	0	0	0	0	0.23	0	0
i4	0	0	0	0.12	0	0	0	0	0	0	0	0	0	0	0
i5	0	0	0	0.45	0	0	0	0.45	0	0.45	0.45	0	0	0.45	0.45
i6	0	0	0	0.45	0	0	0	0.45	0	0.45	0.45	0	0	0.45	0.45
i7	0	0	0	0	0	0	0.45	0	0	0.45	0	0	0	0	0
i8	0	0	0.58	0	0.45	0	0	0	0	0	0	0	0	0	0
i9	0.45	0	0	0.45	0	0.45	0	0	0	0.45	0.45	0	0	0.45	0.49
i10	0.45	0.45	0	0.45	0	0.45	0	0.45	0.45	0.45	0.49	0.45	0.45	0.45	0.45

Note: All rates are in batch/day and i1, i4, i6 and i9 are owned facilities

Table 6.4: Manufacturing yields for industrial case study

	p1	p2	p3	p4	p5	p6	p7	p8	p9	p10	p11	p12	p13	p14	p15
i1	10	1	0	8	0	6	0	10	2	9	7	1	0	12	12
i2	9	0	0	8	0	6	0	9	0	8	10	0	10	12	11
i3	0	0	0	0	0	0	0	0	0	0	0	0	9	0	0
i4	0	0	0	9	0	0	0	0	0	0	0	0	0	0	0
i5	0	0	0	10	0	0	0	10	0	8	8	0	0	11	11
i6	0	0	0	12	0	0	0	10	0	8	17	0	0	17	14
i7	0	0	0	0	0	0	10	0	0	10	0	0	0	0	0
i8	0	0	36	0	10	0	0	0	0	0	0	0	0	0	0
i9	10	0	0	12	0	5	0	0	0	8	16	0	0	12	13
i10	9	1	0	12	0	5	0	10	2	8	14	1	10	12	12

Note: All yields are in kilograms/batch and i1, i4, i6 and i9 are owned facilities

Table 6.5: Manufacturing costs for industrial case study

	p1	p2	p3	p4	p5	p6	p7	p8	p9	p10	p11	p12	p13	p14	p15
i1	1	1	0	10	0	3	0	1	1	1	3	1	0	1	1
i2	10	0	0	5	0	2	0	5	0	10	2	0	2	5	2
i3	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0
i4	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
i5	0	0	0	20	0	0	0	20	0	20	20	0	0	5	20
i6	0	0	0	10	0	0	0	10	0	10	10	0	0	1	10
i7	0	0	0	0	0	0	10	0	0	10	0	0	0	0	0
i8	0	0	1	0	5	0	0	0	0	0	0	0	0	0	0
i9	10	0	0	10	0	10	0	0	0	10	8	0	0	1	10
i10	15	15	0	15	0	15	0	15	15	15	15	15	15	15	15

Note: All costs are in rmu's and i1, i4, i6 and i9 are owned facilities

Table 6.6: Parameter data for industrial case study

Price/Cost	*Unit*	*Value*
Production lead time	days	14
Product lifetime	time periods	8
Sales price	rmu/batch	20
Storage cost	rmu/batch	0.1
Lateness penalty	rmu/batch	0.1
Changeover cost	rmu/batch	2
Backlog decay	unitless	0.5

6.5.2. Demand Analysis and Risk Constraint Impact

The industrial case is formulated using the single objective model detailed in Section 4.1 and using the data shown above the "base case" problem is solved. The base case is solved twice, with and without the risk constraint activated, whereby the set of products that can be produced in more than one facility and are seen to be of considerable strategic importance includes p1, p4, p6, p10, p11 and p13. This is repeated for two other demand scenarios, low demand (50% of the base case demand) and high demand (150% of the base case demand).

The computational results and key performance measures are shown in Table 6.7, and include: total product demand (kg), total product sales (rmu), total operating costs (rmu), total profit (rmu), customer service level (CSL) which is the percentage of batches which are met on time, average utilisation (UTIL) of owned sites, and sales to demand ratio (S/D) which is the proportion of total demand that is met by the end of the fifteen year time horizon.

In the base case the risk constraint is found to result in a 2.7 % increase in operating costs due to the extra operating costs (changeover and manufacturing) incurred as a result of the additional campaigns required in order to satisfy the risk constraint. The impact on sales, profit, CSL and S/D equate to around a 1.5 % drop. This represents the operational cost of the "piece of mind" that is gained through the dual facility production, as this hedges against facility outages throughout the time horizon by offering cost and time saving flexibility, for example, in the case of a last minute production plan reconfiguration. The impact of the risk constraint is seen to be considerably lower in the sales, cost, profit, CSL and S/D measures (one order of magnitude) in the low demand scenario and considerably higher in the high demand scenario (approximately 5 fold), as a result of the respective excess and lack of manufacturing capacity. This leads to the conclusion that the decision whether to enforce the risk constraint is restricted by the level of expected product demand. For example, in the case of the low and base demand scenarios allowing for risk would likely be acceptable as the impact may well be seen to be negligible from a cost-benefit perspective. While in the case of the higher demand this would be

unacceptable as the 77.9% expected CSL would probably seem too much of a sacrifice given the 10.6% drop from the 87.1% expected CSL.

The changing customer service levels as compared with the total base case demand over time are shown for each scenario in Figure 6.1. The most noticeable feature of Figure 6.1 is that of the low CSL in both the high demand scenarios (Figure 6.1a (▲) - without risk and Figure 6.1b (▲) - with risk). Until the year 2016 the CSL is well below 95% which can be explained by the trend in total demand shown in Figure 6.1c. It is also noted that in the "with risk" scenario all CSL's are lower than in that of the "without risk" scenario most notably in the high demand scenario.

Figure 6.2 shows the capacity utilisation for each facility for each of the demand scenarios that results in the maximum profit. Facilities i1, i4, i6 and i9 are the most well utilised facilities in each of the demand scenarios which can be explained by the lower cost of manufacturing. Facilities i7 and i8 (both contract manufacturers) are not well utilised mainly due to the fact that they each can only make 2 products in the portfolio, which each have relatively low demands. Given the higher costs associated with securing CMO capacity, these results highlight that the time booked with these CMOs should be renegotiated to avoid paying for idle capacity.

Table 6.7: Performance measures at each demand scenario and the impact of the risk constraint for the industrial case study

	Demand (kg)	**Sales (rmu)**	**Cost (rmu)**	**Profit (rmu)**	**CSL (%)**	**UTIL (%)**	**S/D**
Low	$5.94x10^3$	$1.19x10^4$	$3.09x10^2$	$1.16x10^4$	99.8	62.3	0.99
Low/risk	$5.94x10^3$	$1.19x10^4$	$3.11x10^2$	$1.16x10^4$	99.7	63.5	0.99
%Difference	**0**	**- 0.1**	**0.3**	**- 0.1**	**- 0.1**	**1.9**	**- 0.1**
Base	$1.19x10^3$	$2.37x10^4$	$1.00x10^3$	$2.27x10^4$	99.3	86.4	0.99
Base/risk	$1.19x10^3$	$2.34x10^4$	$1.03x10^3$	$2.33x10^4$	97.7	85.4	0.98
%Difference	**0**	**- 1.3**	**2.7**	**- 1.4**	**- 1.6**	**- 1.2**	**- 1.2**
High	$1.78x10^3$	$3.17x10^4$	$1.56x10^3$	$3.02x10^4$	87.1	96.2	0.89
High/risk	$1.78x10^3$	$2.99x10^4$	$1.41x10^3$	$2.84x10^4$	77.9	95.3	0.84
%Difference	**0**	**- 5.9**	**9.8**	**- 5.7**	**-10.6**	**- 1.0**	**- 6.0**

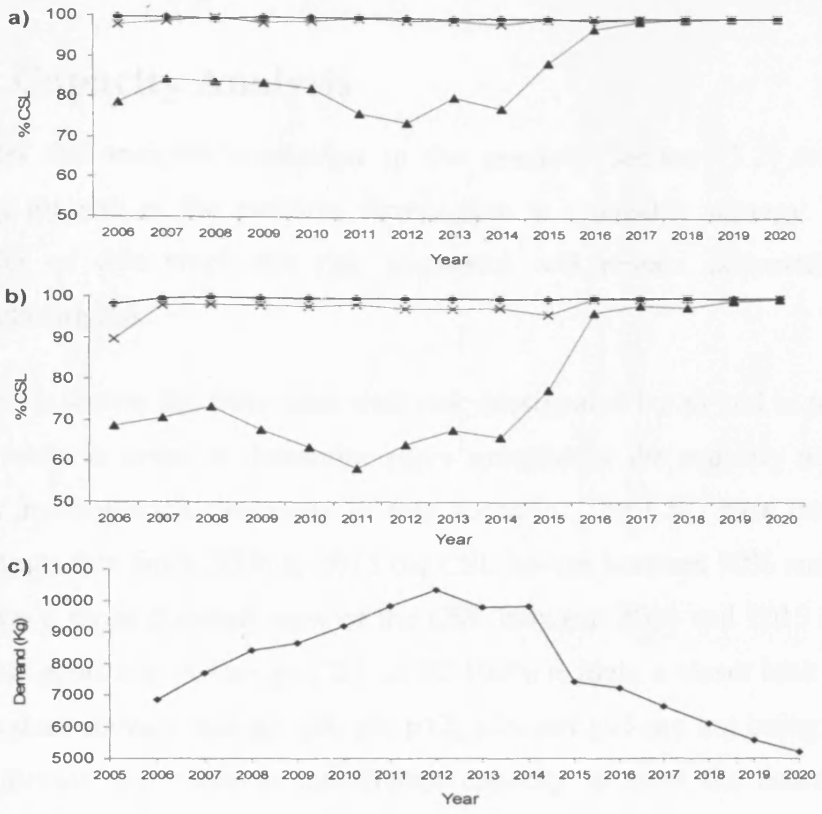

Figure 6.1: Customer service level for the low (♦), base (x) and high (▲) demand scenarios without (a) & with (b) the risk constraint activated. (c) shows the total base case demand for comparison.

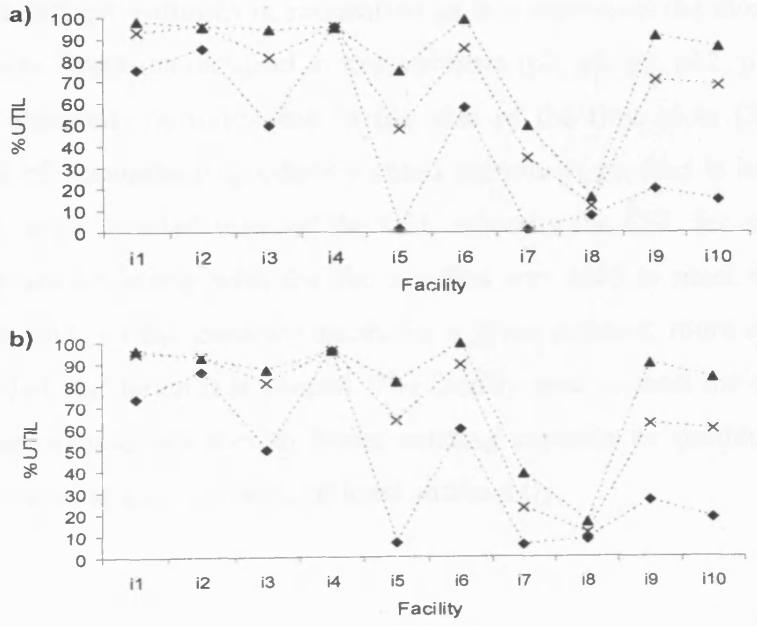

Figure 6.2: Capacity utilisation for each facility for the low (♦), base (x) and high (▲) demand scenarios without (a) & with (b) the risk constraint activated. Owned facilities are i1, i4, i6 and i9.

6.5.3. Capacity Analysis

Based on the analysis conducted in the previous section (5.2) we assume that allowing for risk in the problem formulation is a sensible strategy. Hence for the remainder of this work the risk constraint will remain activated allowing for manufacturing risk.

Figure 6.1b shows the base case with risk (designated by x) and is now considered more closely in order to determine more specifically the capacity needs and likely capacity management decisions in this scenario. The CSL base demand scenario curve shows that from 2006 to 2015 the CSL hovers between 90% and 100%. Figure 6.3 shows a more detailed view of the CSL between 2006 and 2015 for each of the individual products. Although CSL of 90-100% is high, a closer look at the CSL for each product reveals that p2, p8, p9, p12, p14 and p15 are not being fully satisfied. This indicates that there is insufficient capacity to meet the demands of all the products. The fact that the optimisation results show some product demands met fully and some not at all (i.e. p2 and p8) can be attributed to the mathematically driven nature of the model whereby the manufacture of the product with the lowest costs and the highest volumes is maximised as this represents the most cost-effective use of capacity. Products required in low volumes (p2, p8, p9, p12, p14 and p15) are avoided (or delayed) partially due to the size of the time slots (3 months), as a commitment of 3 months to produce a small volume of product is inefficient. Table 6.8 shows a more detailed view of the CSL whereby the CSL for each product for each year is shown along with the facility that was used to meet the orders. This gives a better idea of the capacity needs for a given product, more specifically how much is needed and when it is needed. The facility used to meet the orders may help manufacturers decide whether to boost existing capacity or produce elsewhere or whether contract capacity is being utilised sufficiently.

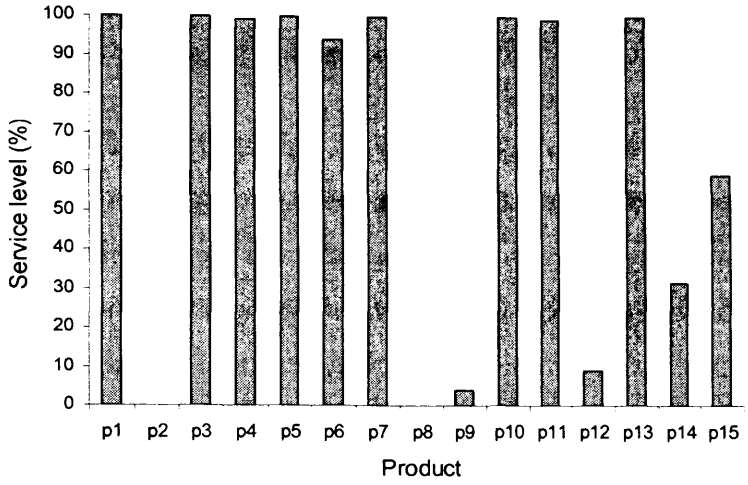

Figure 6.3: Average customer service levels for the individual products between 2006 and 2015.

Table 6.8: Actual customer service level for each product at each year between 2006 and 2015.

Year	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
p2	0	0	0	0	0	0	0	0	0	0
p8	0	0	0	0	0	0	0	0	0	0
p9	0	0	0	0	0	0	0	0	0	i1/ 100
p12	0	0	0	0	0	0	0	0	0	i1/ 68.6
p14	0	0	i6/ 100	i6/ 100	0	0	0	0	0	i5/ 100
p15	0	0	0	0	0	0	i1/ 100	i1/100	i5/ 90.9	i5/ 100

Note: i's denote facilities where products for that order where produced.

6.5.4. The Impact of Multiple Objectives and Different Operating Policies

The model was adapted to a goal programming formulation as detailed in Section 4.2 to account for multiple objectives where deviations from target values of each objective were minimised. There are numerous policies which can be adopted to guide strategic planning decisions. In our study we assume that all policies have the same target levels for each of the objectives namely the minimisation of costs to a target level of 100,000 rmu's, the maximisation of CSL to a target level of 100%, and the fulfilment of a capacity utilisation target of 90% for all owned facilities.

Here, three different scenarios are adopted which differ in the relative importance set for each objective, and are explained below:

- Cost policy (COST): This policy is that of the cost-conscious decision-maker who may have costs targets to meet and which cannot be exceeded under any circumstances, irrelevant of the CSL achieved. An additional objective includes the need to meet set capacity utilisation targets. The weighting of the objectives COST:CSL:UTIL in this case is 7:1:2.

- CSL policy: This policy is that of the customer-conscious decision-maker who feels that the maximisation of service levels is of such great importance that exceeding cost targets to improve CSL is an acceptable sacrifice. An additional objective also includes the need to meet set capacity utilisation targets. The weighting of the objectives COST:CSL:UTIL in this case is 1:7:2.

- Compromise policy (COMP): This policy is that of the compromising decision-maker who would like to meet each of the set goals equally and aims to satisfy cost targets while achieving high service levels and meeting utilisation targets. The weighting of the objectives COST:CSL:UTIL in this case is 1:1:1.

Note that the utilisation objective is weighted as 2 in the cost and CSL policies as both the negative and positive deviations are penalised in the objective function, while in the cost policy only the positive deviation is penalised and in the CSL policy only the negative deviation is penalised.

Figure 6.4 shows the percentage deviation from the goal targets for each of the base case and each of the operating policies and Figure 6.5 shows a plot of the operating costs and service levels for each of the policies. It should be noted that the highest deviation in cost and utilisation are attained in the base case, where the reason for this is that the base case is modelled using the single objective problem (maximisation of profit) and does not directly attempt to meet these objectives. Analysis of the three operating polices shows that the CSL policy followed by the COMP and COST policies achieves the highest service level. While both the COST and the COMP policies meet the costs target levels exactly, the CSL policy shows a

slight deviation 0.5%. All policies sufficiently meet the utilisation target. In terms of profit there is no significant difference relative to the base case as the CSL policy matches the base case and the COST and COMP policies make only a 1% drop. Hence a high profit is still achieved while also satisfying key cost, CSL, and UTIL targets more closely.

Further computations were conducted for all policies at two additional cost target levels of 90,000 and 110,000 rmu in order to analyse the problem sensitivity. Figure 6.6 shows the resulting plot of operating cost and service level. The aim in both Figures 6.5 and 6.6 is to lie as close to the bottom right hand corner of the graph as possible, signifying the lowest costs and highest service level. A similar trend can be seen at each of the cost target levels whereby the CSL policy achieves the highest service level, followed by the COMP and COST policies and only the COMP and COST policies meet the required cost targets. The difference in performance is more evident as cost targets are tightened, reflecting the difficulty of achieving high service levels at lower costs. This observation motivated further sensitivity studies on the cost and service levels, which is conducted using the COMP policy by incrementally changing the cost target level and the associated plot is shown in Figure 6.7. This graph shows a clear trend of an increase in service level with an increase in cost up to a cost target of 100,000 rmu's, at which point service levels stagnate at around 98%. The further increase in cost without an increase in service level is attributed to the production of orders of backlogged batches, which even though they are of lesser importance than new orders, contribute to cost through late penalties and hence are manufactured only if monetary resources are available.

Finally, while the optimisation framework presented can be used as a production planning tool, it is best used as a capacity analysis tool for aiding strategic manufacturing capacity related decisions. In reality demands would not all be due at the end of the year, and better demands forecasts would likely be available as demand dates neared.

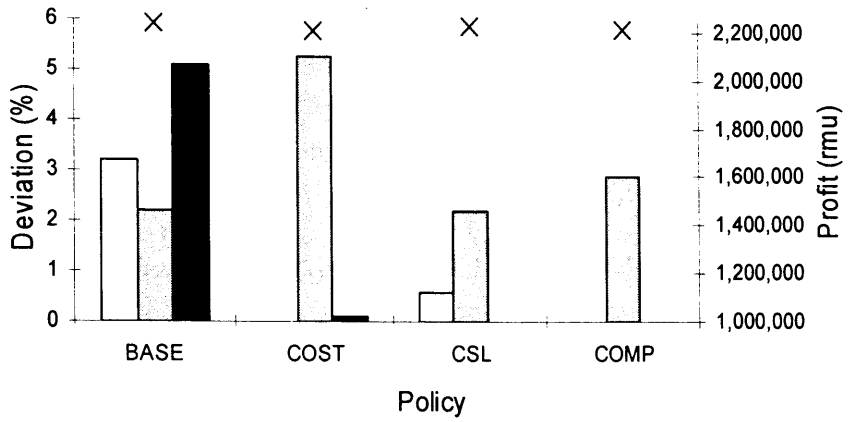

Figure 6.4: Percentage deviation from each of the cost (white), service level (grey) and utilisation (black) goals for the base case, cost, customer service level and compromise operating policies and the profit (x) achieved by each policy.

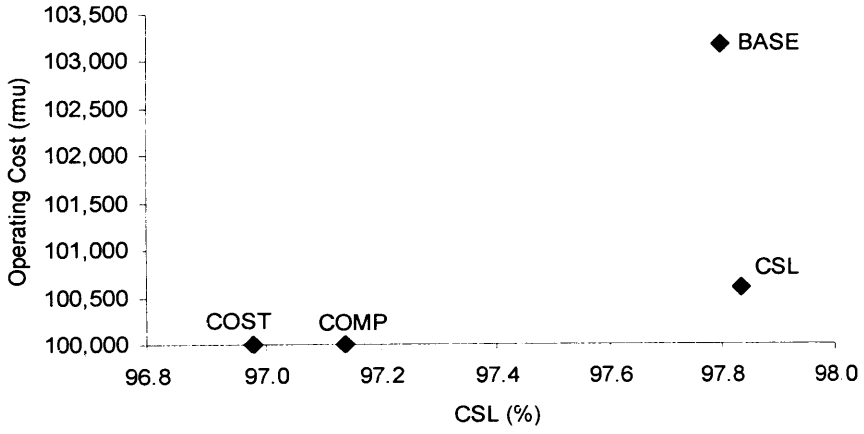

Figure 6.5: Shows the operating cost and service levels for the base case, cost, customer service level and compromise operating policies.

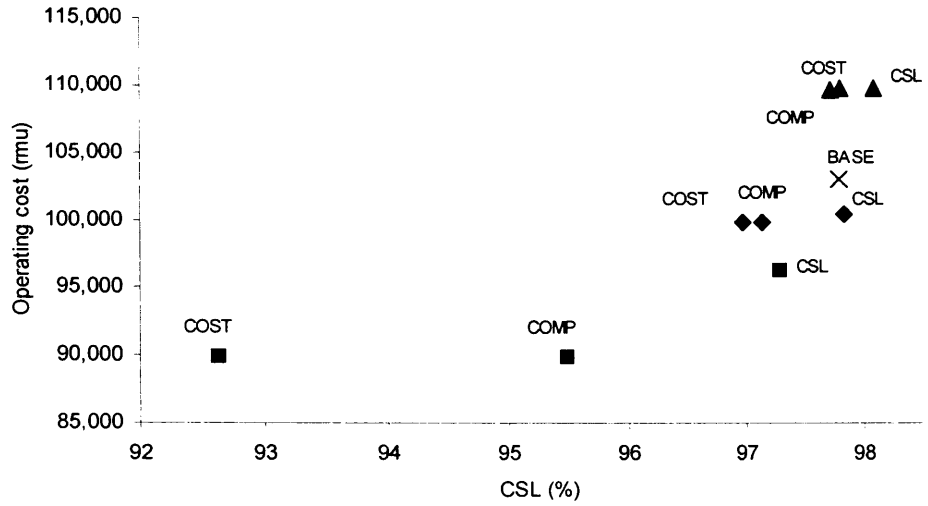

Figure 6.6: Operating cost and service levels for the base case, cost, customer service level and compromise operating policies at different cost targets, 90, 000 (■), 100, 000 (♦),and 110, 000 (▲), and the base case (x).

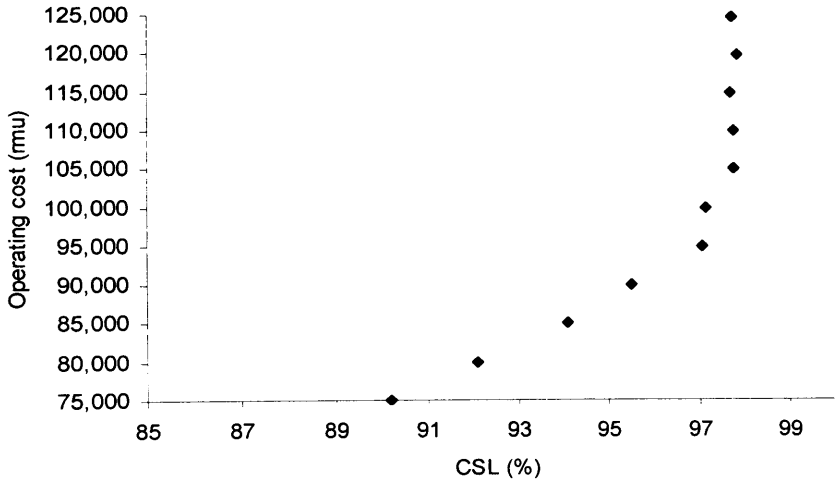

Figure 6.7: Sensitivity study of the operating cost and service levels for the compromise policy.

6.6. Conclusions

An optimisation-based framework for long term planning of biopharmaceutical manufacture has been presented, and tested on an industrial case study. The problem was first solved as a single objective problem, where profit was maximised, and a capacity analysis was conducted to determine where additional capacity would be needed. The problem was then extended to allow for multiple objectives via goal programming, namely operating costs, customer service levels and capacity utilisation of owned facilities. Three different operating policies were compared, namely a cost biased (COST), service level biased (CSL) and a compromising policy (COMP). CSL was found to outperform all polices in achieving the highest service level. Only the COST and COMP policies met cost targets with COMP achieving the higher service level of the two approaches. Sensitivity studies were conducted on cost targets and showed a similar trend to that noted above, with the trend becoming more evident with lower cost targets. Further sensitivity analysis was conducted on the COMP scenario considering different cost targets and monitoring service levels which were found to increase with increasing operating costs and hence monetary resources eventually reaching a plateau. Capacity analysis of an industrial case study has been shown to give decision makers a better idea of what their existing capacity situation is and where it may need capacity increases or improvements. The approach has also been demonstrated to help evaluate different operating polices and quantify operational performance at different monetary resource levels.

6.7. Nomenclature

Indices

b	timeblock
dev	negative (*neg*) or positive (*pos*) goal deviation
g	goals: *cost*, *csl* (customer service level), *util* (capacity utilisation)

i	facility
p	product
t, θ	time periods

Sets

DT	set of time periods in which product demands are due.
IP_p	set of facilities i manufacturing product p.
OS	set of owned facilities.
PI_i	set of products p produced by facility i.
RS	set of product which must be produced in at least two different facilities.
TB_b	set of time periods in a time block b.
TI_i	set of time periods t in which facility i is available for use.

Parameters

C_{ip}	storage capacity of product p at facility i, batches
D_{pt}	demand of product p at time period t
GT_g	aspired goal target for goal g
r_{ip}	production rate of product p *at facility* i, batches per unit time
H_t	available production time horizon over time period t
T_{ip}^{max}	maximum production time for product p
T_{ip}^{min}	minimum production time for product p
yd_{ip}	yield conversion factor, kilograms per batch

$WT_{g,dev}$ Archimedean weight of goal deviation

α_{ip} lead time for production of first batch of product p at facility i

ζ_p life time of product p, number of time periods t

υ_p unit sales price for each batch of product p

η_p unit cost for each batch produced of product p

ψ_p unit cost for each new campaign of product p

δ_p unit cost charged as penalty for each late batch of product p

ρ_p unit cost for each stored batch of product p

π rate of backlog decay

Binary Variables

Y_{ipt} 1 if product p is produced over period t at facility i; 0 otherwise

Y_{ipb}^{new} product p is produced over block b at facility i; 0 otherwise

Z_{ipt} 1 if a new campaign of product p at facility i is started in period t; 0 otherwise.

Continuous Variables

I_{ipt} amount of product p stored over period t at facility i

$GD_{g,\,dev}$ actual goal difference for each goal deviation

$GD_{g\,dev}^{norm}$ normalised goal difference for each goal deviation

GL_g achieved goal level for goal g

GL_g^{norm} normalised goal level for goal g

GLT_{gt} achieved goal level for goal g at time period t

GLI_{gi} achieved goal level for goal g at facility i

K_{ipt} amount of product p produced over period t at facility i (kg)

$Prof$ expected operating profit

S_{pt} amount of product p which is sold over period t

$Sumd$ sum of adverse deviations

T_{ipt} production time for product p at time period t at facility i

Tf_{it}^{tot} total production time over period t at facility i

W_{pt} amount of product p wasted over period t

Δ_{pt} amount of product p which is late over period t

Integer Variables

B_{ipt} amount of product p produced over period t at facility i (batches)

Chapter 7

Commercial Considerations for the Development of a Software Tool for Production Planning of Biopharmaceutical Manufacture

7.1. Introduction

In this chapter, an implementation plan of a potential commercialisation route for the work generated in this EngD is presented. The development of the model, appropriate software architecture, implementation issues, estimated project resource requirements and potential benefits are discussed. The model implementation is based on a typical biopharmaceutical industry production planning problem, whereby a biopharmaceutical manufacturer wishes to optimise the production plans of a biomanufacturing facility or network of facilities using a hybrid simulation/optimisation approach.

7.2. Model Development

The EngD project presented in this thesis was collaborative between UCL's department of Biochemical Engineering and BioPharm Services UK. Its objective is to provide biopharmaceutical manufacturers with an optimisation framework for the production planning of multiproduct facilities. An intellectual property (IP) agreement for the rights to the resulting mathematical formulations was drawn up and agreed by all parties involved.

After considerable academic and industrial surveying in close collaboration with BioPharm Services UK, the project was defined. Over the subsequent four years, mathematical formulations along with algorithms for their solution were developed and tested on realistic example industrial problems. The results were presented at both national and international conferences.

7.3. Model Architecture

The first stage in taking the project from a theoretical mathematical formulation to a practical industrially applicable decision support tool is embedding the model in a practical/familiar software application infrastructure. The components of any potential system should include the following:

- A simulation package for the detailed formulation of problem features and graphical representation of the results (e.g. Extend, Promodel).
- A database or spreadsheeting application for the specification of input parameters and a platform for the return of generated results (e.g. Microsoft's Access).
- A modelling environment for the specification of the mathematical optimisation model (e.g. GAMS or ILOG's OPL development studio).
- An optimisation solver for the solution of the MILP models (CPLEX or XPRESS).

The selected applications must have a compatible application programming interface (API) for software integration. An API is the interface that a computer system, library or application provides in order to allow requests for service to be made of it by other computer programs and to allow data to be exchanged between them. Relevant example API's include: open database connectivity (ODBC), component object model (COM) and programming languages C and C++.

A detailed survey of commercial optimisation tools was conducted, and included an assessment of features, pricing information and interfacing capabilities. An assessment for tool selection and a solver comparison were also conducted (Appendix 1).

A diagrammatical representation of the required software infrastructure is shown in Figure 7.1 below.

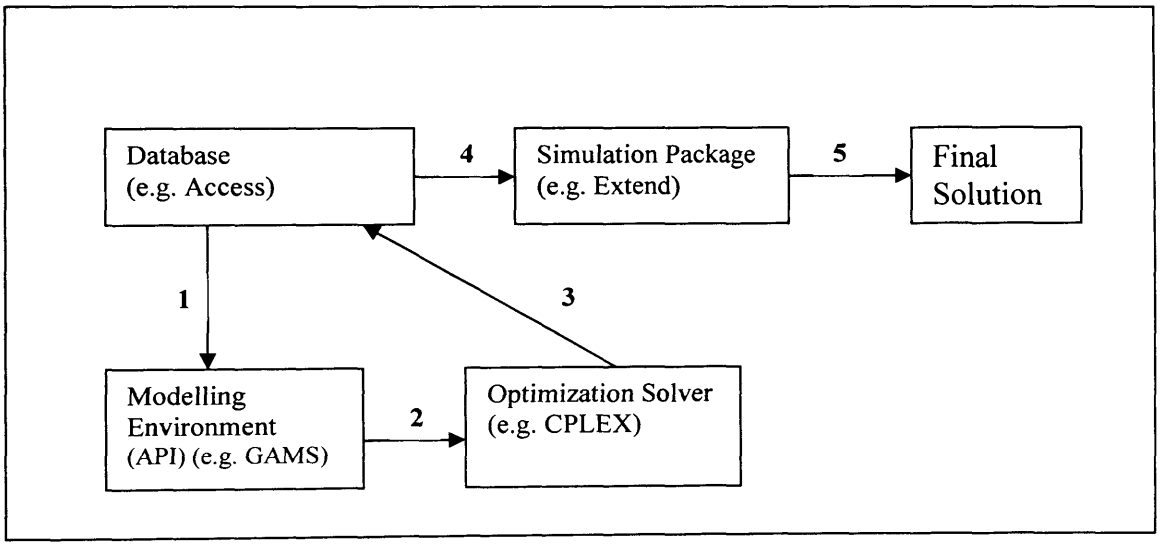

Figure 7.1. A diagrammatic representation of the information flow within the software infrastructure.

An explanation of steps 1 – 5 in Figure 7.1 is given below:

1. Once problem inputs (parameters) have been specified and appropriately set up in the database system, the data is imported by the modelling environment. The database communicates with the modelling environment via an API to set up the problem and perform the optimisation.

2. A preformulated model with appropriate data import/export commands then accepts the input data and submits the problem with the relevant solution and display commands/conditions to the solver.

3. Upon solution termination/convergence (either by achieving required solution quality or exceeding allowable solution time) a solution is returned and sent to the database system for appropriate data manipulation.

4. The data is submitted to the simulation package for validation of the solution feasibility/quality, the simulation should be dynamically/programmatically scripted to match the problem.

5. The final solution output may be in the form of raw data to a database system for further manipulation and/or graphical interpretation via a Gantt chart, e.g. Microsoft PROJECT.

7.4. Project Implementation

An example implementation scenario is presented which involves a client (e.g. a large-scale biopharmaceutical manufacturer) who approaches a team of biopharmaceutical industry consultants for the development of a production planning tool.

A chronological implementation plan of the project's key phases is presented and has a similar structure to a typical software development project as shown below:

7.4.1. Phase 1: User Requirements Analysis

- Client visit (1): Consultants visit client site to gain understanding of detailed user specifications.

- Timing: Create a project schedule.

- Contracts: Establish a project contract covering key issues such as confidentiality, financials, delivery and penalties.

- Basic Functional Spec: A basic functional specification of the software is developed to meet the requirements of the client.

7.4.2. Phase 2: System Design and Development

- Client visit (2): Consultants visit client site to qualify that the functional spec meets client requirements. Information and data collection.

- Full Functional Spec: A fully functional specification of the product is developed.

- Validation: Product is validated using historical data.

- Testing: product must conform to standard alpha and beta testing standards.

- Documentation: Appropriate product user manual/documentation must be developed and validated.

7.4.3. Phase 3: Operation and Maintenance

- Client visit (3): Deployment at client site: Handover of product and installation at client site.

- Training: Users must be trained at client site.

- Maintenance: Agreements for appropriate maintenance at contract specification stage may or may not be included (Quality assurance guarantees).

7.4.4. Project Costing

Resource requirements and costs have been estimated based on a typical industrial project, and presented for all phases of implementation. An approximate project costing was based on some assumptions as shown below:

- Consultants conducting the work are charged at £50 per man hour and assumed to work a 40 hour week.

- We assume the consulting company conducting the work owns a copy of all necessary developmental software tools/licences. Hence client is charged for a copy of an end user (runtime) product licence and does not include annual maintenance or support fees.

- No mark up is included in the cost estimate as this will depend on the consulting company's business strategy.

- A survey of optimisation tools was conducted and aids the developer in gaining a better understanding of available software capabilities. This was not charged.

- Table 7.1 shows the approximate project costing which totals *£ 47, 980* and total project duration of *20 weeks*.

Table 7.1. Project costing and task durations.

	All costs in UK pounds	
Task	**Resource**	**Cost (£ - British pounds)**
	(labour is calculated as man-weeks)	
Phase 1: User Requirements Analysis (Duration: 7 weeks)		
Client visit (1)	Consultants 1 week	2,000 + 1000 (expenses)
Basic functional spec	Microsoft Access (database)	130
Basic functional spec	Extend (simulation package)	50 (run time licence)
Basic functional spec	GAMS (modelling system)	1,600
Basic functional spec	XPRESS (solver)	3,200
Basic functional spec	GUI (external consultants 1 week)	1,000
Development work	Consultants 5 weeks	10,000
Phase 2: System design and development (Duration: 11 weeks)		
Client visit (1)	Consultants 1 week	2,000 + 1,000 (expenses)
Development work	Consultants 8 weeks	16,000
Documentation	Consultants 2 weeks	4,000
Phase 3: Operation & Maintenance (Duration: 2 weeks)		
Client visit (1)	Consultants 1 week	2,000 + 1,000 (expenses)
Training	Consultants 1 week	2,000 + 1,000 (expenses)
TOTAL COST (Total duration: 20 weeks)		47,980

7.5. Potential Benefits to Client

Manufacturers wishing to improve their planning and scheduling decisions can potentially achieve vast financial benefits by improving capacity utilisation and cost effectiveness. Saraph (2001) reports direct benefits from a 2 month long capacity analysis project of a Bayer Corporation biomanufacturing facility amounting to $1,100,000. It has been estimated (Mallik *et al.*, 2002) that a typical mammalian cell-culture facility can increase annual revenues by $380 million with a 25% increase in plant utilisation. Thus these examples further reinforce the possible savings improvements in scheduling and planning decisions can help achieve.

Chapter 8

Validation Issues

8.1. Introduction

In the biopharmaceutical industry each step of any process with a direct impact on the final product must be validated by the appropriate regulatory authority for the geographic region where it will be licensed. Validation is defined by the FDA (Food and Drug Administration) as "Establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality attributes". Validation requires the enforcement of manufacturing guidelines and regulations. In the biomanufacturing industry a process is said to be compliant with Good Manufacturing Practice (GMP), a set of regulations, codes, and guidelines for the manufacture of drugs, medical devices, diagnostic products, foods products and Active Pharmaceutical Ingredients (APIs).

Aside from validation being a legal requirement, it also brings many benefits to a manufacturer. Some typical benefits of the validation process include:

- Increasing the understanding of a system or process.
- Ensuring the safety and efficacy of a manufactured product.

- Producing evidence of and enforcing set quality control (QC) criteria.
- Enhancing the credibility of analytical data if a batch is questioned.

Given the nature of this EngD thesis, the following section will focus on the validation of software systems.

8.2. Software Validation

Software validation cannot be ignored as it may influence a part or all of a given process. Any software system which performs a regulated function must have its production, control, review and operation validated.

General guidelines for manufacturing software validation are presented in the Good Automated Manufacturing Practice (GAMP) guidelines. Whether applied within GMP (Good Manufacturing Practice), GCP (Good Clinical Practice) GLP (Good Laboratory Practice) or GDP (Good Distribution Practice) these validation guidelines provide the user and/or supplier of a software system with a valuable framework for the production and use of compliant validated bioprocess software.

An overview of the validation process is shown below:

- Planning: Prepare a written validation plan.
- Specification: Specify and agree what is required. Perform design reviews.
- Test planning: Prepare document to describe how the equipment/system is to be tested (includes Installation qualification (IQ), operational qualification (OQ) and performance qualification (PQ)).
- Testing: Perform tests and collect results (IQ, OQ and PQ).
- Review and Report: Review results to show that system performs as specified, report conclusions, plus any reservations.

Some benefits of the GAMP validation process include:

- Reducing time and costs taken to achieve compliant systems.
- Eliminating the need for expensive retrospective validation.
- Providing better visibility of projects to ensure delivery on time, on budget, and to agreed quality standards.
- Clarifying the division of responsibility between the user and the supplier.
- Providing cost benefits, by aiding the production of systems that are fit for purpose and meet user and business requirements.

The validation procedures and benefits shown above are applicable to the majority of automated systems in the biopharmaceutical industry. However, not all software employed within the biopharmaceutical industry performs a regulated function.

8.3. Decision Support Systems

Regulatory authorities enforce only that systems which perform a "regulated" function must be validated, examples include automated and online control and operation software.

The work presented in this thesis does not perform a regulated function and hence falls into the category of decision support systems, which includes systems such as planning, scheduling, process simulation and supply chain optimisation tools, which are often used for "what if" decision making analysis or for the generation of production plans or operating schedules. Such tools do not have a direct effect on the manufacturing process as they are only used to aid the decision maker or operator. Hence, such tools are exempt from the bioprocess/biomanufacturing validation process.

Decision support systems will however generally be expected to undergo software validation in the final stages of their development, where it is generally referred to as software testing. Software testing is a process used to help identify the correctness, completeness, security and quality of newly developed computer software. These tests include standard testing such as alpha and beta testing which is used for the debugging of software and ensuring user specified requirements are met.

While, implementation of the work generated in this EngD will not require validation directly, there are some important considerations which are affected by the validation process. Some indirect validation issues are discussed below:

- Manufacturing specific considerations: modelling of the relevant manufacturing consideration must be accounted for. e.g. if a certain facility is validated to certain specifications, such as suite specific product manufacturing, this must be represented accurately or production plans will be infeasible.

- Decision support not decision-making: many validation related issues are not accounted for in the modelling framework. While a given production plan may be optimal in the mathematical sense, issues such as the risk of contamination and the high validation costs associated with frequent changeover may not be accounted for.

8.4. Conclusions

The validation process is a legal requirement, with many benefits to the manufacturer, however is not applicable to decision support systems such as those presented in this EngD thesis. However, as with the majority of software products, decision support systems are required to meet certain software testing standards, and those used in the biomanufacturing industry are no exception.

Chapter 9

Conclusions & Future Directions

Operating multiproduct facilities in the biopharmaceutical sector poses several challenges for planning and scheduling. Significant economic benefits may be expected if these can be overcome (Gosling, 2003). A survey of academic work involving the application of mathematical programming to production planning in the process industries identified a distinct lack of work in bioprocessing. Hence, the aim of this thesis was *to facilitate the biopharmaceutical industry's strategic and operational decision-making by applying mathematical programming techniques for production planning of biopharmaceutical manufacturing facilities.* Towards that goal, a number of optimisation-based frameworks have been developed in order to assist decision-makers in the biopharmaceutical industry. The key contributions of the thesis are summarised in Section 9.1, while Section 9.2 suggests promising new directions for future research work.

9.1. Contributions of this Thesis

The contributions of this thesis will be presented for each of the research Chapters (3-8) and are as follows.

9.1.1. Medium term Planning of Biopharmaceutical Manufacture

The aim of Chapter 3 was the determination of the optimal medium term production plans for a multiproduct, multi-suite biopharmaceutical manufacturing facility by capturing the characteristic bioprocessing features of the production planning problem in the biopharmaceutical industry.

A mathematical programming approach using a mixed integer linear programming (MILP) formulation for medium term planning of biopharmaceutical manufacture was presented. An improved formulation was used to represent and solve two illustrative examples. The solutions obtained using the mathematical programming approach were compared to those generated by an industrial rule based (IRB) approach which demonstrated the value of the proposed approach. In both examples considered, the mathematical programming approach was shown to outperform IRB in terms of profitability. The profitability achieved by MP was considerably higher demonstrating the necessity for calculated decisions regarding campaign changeovers and inventory profiles. This confirmed the ineffectiveness of IRB approaches for solving larger more complex planning problems. The proposed mathematical programming approach offers an improved alternative to industrial rule-based methods for medium term planning of biopharmaceutical manufacture and presents biomanufacturers with a business decision support tool to aid in production/capacity planning and obtaining longer term strategic decisions.

9.1.2. Medium term Planning of Biopharmaceutical Manufacture under Uncertainty

The challenges of incorporating the impact of uncertainty in biopharmaceutical manufacturing production plans were addressed in Chapters 4 and 5. Mathematical programming formulations were developed and assessed for their suitability in determining the optimal medium term production plans for a multiproduct biopharmaceutical manufacturing facility given uncertain fermentation titres. Solutions were required to be achieved within a reasonable computational time without compromising significantly the quality of the obtained solution.

9.1.2.1. *Medium term Planning of Biopharmaceutical Manufacture using Two-Stage Programming*

Initially, the problem was formulated as a two-stage programming model and an iterative algorithm was proposed for the problem's efficient solution. The example problems presented in Chapter 4 were all solved using a deterministic model, a full-space two-stage programming model, a rolling horizon algorithm and a proposed construction/improvement algorithm (CON/IMP). The impact of uncertainty on the solution schedules was quantified for both examples via Monte Carlo simulation. The results showed that CON/IMP consistently matched or exceeded the solution quality achieved by the full space model and the rolling horizon algorithm while making considerable improvements on the deterministic model. This is a valuable framework for biomanufacturers wishing to improve their medium term decision making capabilities by incorporating and addressing the impact of uncertain parameters within their manufacturing schedules. The approach would also likely be of much value in other applications of two-stage programming as it is relatively generic in its nature.

9.1.2.2. *Medium term Planning of Biopharmaceutical Manufacture using Chance Constrained Programming*

An alternative mathematical optimisation-based framework for capturing uncertainty was presented in Chapter 5. As an alternative to multiscenario type representations a chance constrained approach was proposed for tackling variability in fermentation titres when planning biopharmaceutical manufacture. The approach was able to make considerable computational savings and resulted in very good quality solutions when compared with the two-stage programming approach proposed in Chapter 4. Chance constrained programming was demonstrated to be a powerful approach for tackling uncertainty as it was able to generate solutions of the same order of magnitude of those achieved using the deterministic model even for larger problems.

9.1.3. Long term Strategic Planning of Biopharmaceutical Manufacture

The deterministic medium term planning model presented in Chapter 3 was extended to account for long term capacity management of biopharmaceutical facilities. The model was tested on an industrial case study to gain a better understanding of existing capacity capabilities and the quantification of the impact of different strategic operating polices on capacity decisions.

The problem was initially solved adopting a single objective problem formulation, where profit was maximised, and a capacity analysis was conducted to determine where additional capacity would be needed. The problem was then extended to allow for multiple objectives via goal programming, namely operating costs, customer service levels and capacity utilisation of owned facilities. Three different operating policies were compared, namely a cost biased, service level biased and an unbiased compromising policy. The policies were used to demonstrate the differing strategic objectives of biopharmaceutical manufacturers and for the evaluation of different operating polices and quantification of operational performance at different monetary resource levels. Sensitivity studies were used to illustrate the impact of changes in operating costs on customer service levels.

Given the considerable costs and risks associated with capacity planning in the biopharmaceutical industry, the multiobjective optimisation framework presented has demonstrated potential as a useful aid in strategic decision-making for long term planning of biopharmaceutical manufacture. Biopharmaceutical strategic decision-makers are required to make considerable investments in capacity or financial commitments to contract manufacturers years in advance and hence would find such information invaluable in aiding both production and capacity planning decisions.

9.1.4. EngD Commercialisation

An implementation plan of a potential commercialisation route for the work generated in this EngD was presented in Chapter 7. The development of the model, appropriate software architecture, implementation issues, estimated project resource

requirements and potential benefits were discussed. The model implementation was based on a typical biopharmaceutical industry production planning problem, whereby a biopharmaceutical manufacturer wished to optimise the production plans of a biomanufacturing facility or network of facilities using a hybrid simulation/optimisation approach.

9.1.5. Validation Issues

Validation issues relating to this EngD were presented in Chapter 8. In light of the nature of this EngD, issues relating to the validation of software products and decision support systems within the biopharmaceutical industry were discussed here.

9.2. Recommendations for Future Work

The research presented in this thesis has identified a number of issues that need to be further investigated in order to develop more comprehensive optimisation-based frameworks for production planning, capacity planning and general capacity management of biopharmaceutical manufacture.

9.2.1. Deterministic Models

The deterministic MILP model for medium-tem planning of biopharmaceutical manufacture proposed in this thesis was applied to a number of examples to demonstrate its applicability. However there remain some concerns pertaining to the models solution time which increases exponentially with small increases in problem complexity. In order for this model to be combined directly with frameworks for optimisation under uncertainty such as those proposed in Chapters 4 and 5 of this thesis, further work is necessary towards developing more efficient solution procedures for this proposed deterministic model. Tighter problem formulations may be required.

Another potential avenue for further work is multiscale modelling of biopharmaceutical manufacture, e.g. the integration of the proposed medium term planning model with short term scheduling models such as that of Kondili et al. (1993) given that such models have been successfully applied to bioprocess scheduling in the past (Samsatli and Shah, 1996). Integration of long term planning/supply chain formulations with production planning in the medium term would also be a valuable exercise. This would be the next logical step in a more holistic integrated decision making framework for planning and scheduling of biopharmaceutical manufacture.

9.2.2. Medium term Planning of Biopharmaceutical Manufacture under Uncertainty

Chapter 4 and 5 were concerned with generating production plans given uncertain manufacturing conditions in the biopharmaceutical industry. A reduced version of the deterministic model was extended to allow for variable fermentation titres. Further work using discrete-event simulation for the validation of solution schedules via Monte Carlo simulation would also provide a more accurate understanding of the impact of uncertainty on solution schedules.

Two different optimisation-based frameworks for tackling the problem of production planning under uncertainty were developed, namely a two-stage programming approach and a chance constrained programming approach. Issues relating to further development of them are discussed below.

9.2.2.1. Two-Stage Programming

The construction/improvement-based algorithm developed for the efficient solution of the combinatorial problem resulting from the two-stage programming formulations showed much promise in reducing the solution time while generating very good quality solutions. However it was only tested on problems involving one uncertain parameter (fermentation titre). There would be much value in extending the functionality of the approach to tackle problems with additional uncertain parameters, for example, variable demands. The development of an alternative

efficient solution algorithm by modifying the algorithm developed in this thesis may present challenges as the problem size increases with increasing uncertain parameters.

The algorithm presented is somewhat generic and would hence likely be of value in other applications of two-stage programming whereby an insertion/construction type approach could be leveraged. Construction/improvement type algorithms have not previously been adopted in planning and scheduling under uncertainty or related applications within the field of decision-making under uncertainty.

9.2.2.2. Chance Constrained Programming

The Chance constrained formulation presented in Chapter 5 allowed only for uncertain fermentation titres, hence further work is also required on the formulation of models based on chance constrained programming that allow for an increased level of detail when tackling uncertainty. Once of the main challenges envisaged in the development of new chance constrained programming formulations is the complexity that arises due to the joint probability distribution functions which result from the consideration of multiple uncertain parameters.

9.2.3. Strategic Planning Models

The optimisation-based framework for long term strategic planning proposed in Chapter 6 was used for production planning of bulk product manufacture across multiple sites. There would potentially be much value in extending this approach to include not only bulk product manufacture but also secondary manufacturing steps (filling and packaging). The approach can also be extended to allow for different geographic locations through the incorporation of transportation costs and taxation features for an improved representation of the supply chain/multi-site planning problem. Given the considerable detail required, a simulation-based optimisation framework combining mathematical programming and discrete-event simulation is envisaged for tackling the complete supply chain problem.

Another feature of interest in this section and which may be incorporated in each of the models considered in this thesis is multiple production rates at differing costs. The concept of running a facility at different rates resulting in differing manufacturing costs depending on capacity availability is a valid feature of biopharmaceutical manufacture.

Further work on the multiobjective optimisation formulation proposed would be of value, particularly on developing solution procedures for the more efficient solution of the problem and including uncertainty in the formulation. Further objectives may be included in the stochastic version of the problem, such as financial/market risk and robustness. Further experimentation with goal programming as a multiobjective optimisation approach would also be warranted as alternative approaches to weighted goal programming such as lexicographic and Chebyshev goal programming were not exhausted.

A number of optimisation-based frameworks for production planning of biopharmaceutical manufacture have been developed and tested. Historical trends show the biopharmaceutical industry to be slow adopting such decision support tools, but more recently there are indications that the adoption of such tools is accelerating. Such approaches are envisaged to be more widespread by the end of the decade as market pressures continue to increase and the biopharmaceutical industry begins to mature.

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Appendices

Appendix 1

Assessment of Optimisation Tools for Model Commercialisation

Basic Assumptions

The assumption with all the products selected for this survey is that they are:

- Capable of handling MILP optimisation models.
- Compatible with Microsoft's Windows.
- Not limited by problem size (i.e. a maximum number of variables).
- Required only for a single site (licensing).
- Tables A.1 and A.2 show comparisons of modelling environments and solvers.

Background on survey conducted

The tools shown above were selected from a list of tools/vendors compiled for OR/MS Today's 2005 Linear programming software survey (copyright © 2005 by the Institute for Operations Research and the Management Sciences. All rights reserved) as well as direct communication with the vendors.

The modelling environments considered in this survey have all been described as either:

- M: Modelling environment: These packages are typically designed around a computer modelling language for expressing optimisation models, and offer features for reporting, model management and application development. They are often bundled with commercially available solvers at discounted prices and hence allow for straight forward benchmarking, e.g. GAMS, AMPL.

- MI: Integrated modelling environment: These integrated systems provide a modelling environment usually geared towards their own solvers, and a graphical user interface (GUI) for better model management and debugging, and are often termed development studios. Some include a particularly easy to use GUI for straightforward intuitive model building, reducing the volume and complexity of associated computer programming challenges. An example of this is ILOG's OPL Studio.

- Solvers: Commercial and compatible mixed integer programming (MIP) solvers.

*Table A.1: Comparison of modelling environments (*M - Modelling environment, MI - Modelling environment with integrated solvers).*

Product (Vendor)	**Brief Description***	**Compatible Solvers**	**Read/write spreadsheets and databases**	**API's**	**Pricing ($) / (annual maintenance_/ p.a)**	
					Developer License	**End User License**
AIMMS/ (Paragon Decision Technology BV)	MI	CPLEX, XPRESS	Yes	C++ COM	7000 (15%)	6000 (15%)
AMPL/ (AMPL Optimization LLC)	M	CPLEX, XPRESS, FortMP	Yes	C COM	4000 (0)	4000 (0)
AMPL Studio/AMPL COM Object (OptiRisk Systems)	M	FortMP, CPLEX, others	Yes	C COM	4950 (0)	4950 (0)
GAMS (GAMS Development Corporation)	M	CPLEX, XPRESS	Yes	GDX API VB	3200 (0)	(50%) (0)
ILOG OPL Development Studio (ILOG)	MI	ILOG CPLEX, ILOG Solver, ILOG Scheduler	Yes	COM C++	12200 (18%)	12200 (18%)
LINGO (LINDO Systems, Inc)	MI	LINDO API	Yes	C C++	4995 (0)	70% (0)
OML (The Bionetics Corporation)	MI	C-WHIZ	Read spreadsheets only	C	3800 (0)	3800 (0)
TOMLAB (Tomlab Optimization Inc)	MI	CPLEX, XPRESS	Yes	Utilises Matlab's API, (Matlab + COM, C, C++)	900 (20%)	900 (20%)
What'sBest (LINDO Systems, Inc)	MI (Excel addi n)	LINDO API	Read & write spreadsheets only	C C++	4995 (0)	70% (0)
Xpress-MP Suite (Dash Optimization)	MI	Mosel, XPRESS, MPL	Yes	C/C++ JAVA, .Net, VB	5500 (15%)	45% (15%)

Table A.2: Comparison of solvers (0% annual maintenance means that maintenance/upgrades and support is optional).

Product (Vendor)	**Brief Description**	**Products That Link to Product**	**Read/write spreadsheets and database**	**Pricing ($) / (annual maintenance_/ p.a)**	
				Developer License	**Developer License**
C-WHIZ (The Bionetics Corporation)	Simplex and MIP solver	AMPL, MPL, GAMS,	Reads spreadsheets only	2500 (0%)	2500 (0%)
FortMP (OptiRisk Systems)	Simplex, interior point, MIP, quadratic	AMPL, MPL, Tomlab	Read & write text only	2500 (0%)	2500 (0%)
ILOG CPLEX (ILOG)	Simplex, interior point, MIP, network, quadratic	ILOG OPL Studio, AIMMS, AMPL, GAMS, MPL, Tomlab	Reads spreadsheets only	14650 (18%)	14650 (18%)
LINDO API (LINDO Systems, Inc)	Simplex , MIP and quadratic solver	LINGO and What'sBest	Read & write text only	4000 (0%)	70% (0%)
XPRESS Solver Engine (Frontline Systems Inc)	Simplex, interior point, MIP, quadratic	Excel, Tomlab	Yes	6000 (15%)	45% (15%)

Proposed tool selection "Adventurous user"

The proposed tools selection assumes that the user has some computer programming experience, as GAMS has a relatively steep learning curve and requires a reasonable level of modelling skills for use.

In my opinion the best option from a price and performance perspective would be to opt for a modelling environment like GAMS, coupled with a solver like XPRESS or CPLEX (available directly from GAMS), they are priced as in Table A.3.

Table A.3: Associated costs for adventurous user option

Licensing	GAMS	XPRESS	CPLEX
Developer licence	$3200	$7000	$6400
Run time Licence	$1600	$3200	$3500

These solvers are priced considerably lower than development prices from the original solver vendors (e.g. CPLEX from Ilog, developer licence = $14650) as the GAMS marketing model provides runtime solvers licences for GAMS only, as they are embedded in the GAMS architecture and allow only solution of GAMS models and only limited manipulation of the solver options (which in most cases will be sufficient). This also includes no annual maintenance fees.

More user friendly alternative

An alternative would be to purchase a user friendly integrated package like Ilog's OPL Studio, this will have a considerably lower learning curve for model development as it uses an intuitive optimisation programming language with a much less knowledge of computer programming required, reducing typical development time from weeks to days. A developmental copy of OPL studio with a development licence for CPLEX solver would be required for any deployment in an application. The licence needed for the customer would only be a run time licence. An OPL development licence must be purchased if any model development is required (along with another CPLEX development licence). Pricing and annual maintenance data is shown below in Table A.4.

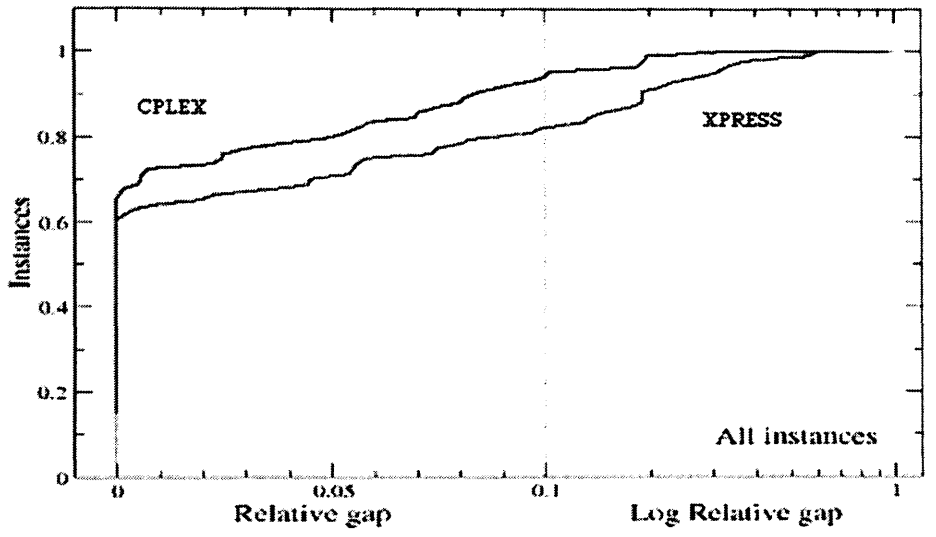
Table A.4: Associated costs for "more user friendly alternative" option

Licensing	ILOG OPL Development Studio Fixed development (Maintenance p/a)	ILOG CPLEX Intermediate Fixed development (Maintenance p/a)
Developer licence	£7,000 (18%)	£8,400 (18%)
Run time Licence	£7,000 (18%)	£4,200 (18%)

Comparison of Solver CPLEX and XPRESS

Ilog's CPLEX and Dash optimization's Xpress solvers are the market leaders. My opinion is that CPLEX is generally faster and may achieve slightly better solution quality. However, there is a difference in price with XPRESS being a little cheaper.

A performance comparison by GAMS is shown below in Figure A.1.



FigureA1: Relative number of instances solved during 1800 s vs. relative gap reached during this time (all instances are counted) (from www.gamsworld.org – benchmarking exercise).

Publications

A number of refereed journal articles were generated throughout the preparation of this EngD thesis.

Journal Articles

Lakhdar, K., Savery, J., Zhou, Y., Titchener-Hooker, N.J., Papageorgiou, L.G. **(2005)**. Medium Term Planning of Biopharmaceutical Manufacture using Mathematical Programming. *Biotechnology Progress* 21, 1478-1489.

Lakhdar, K., Farid, S.S., Titchener-Hooker, N.J., Papageorgiou, L.G. **(2006)**. Medium Term Planning of Biopharmaceutical Manufacture with Uncertain Fermentation Titres. *Biotechnology Progress*, in press.

Lakhdar, K., Papageorgiou, L.G. **(2006)**. An Iterative Mixed Integer Optimisation Approach for Medium Term Planning of Biopharmaceutical Manufacture under Uncertainty. *Chemical Engineering Research and Design,* submitted.

Lakhdar, K., Savery, J., Papageorgiou, L.G., Titchener-Hooker, N.J., Farid, S.S. **(2006)**. Multiobjective Long Term Planning of Biopharmaceutical Manufacturing Facilities. *Biotechnology and Bioengineering*, submitted.

Conference Articles

Lakhdar, K., Zhou, Y.H., Savery, J., Titchener-Hooker, N.J., Papageorgiou, L.G. **(2005)**. Medium term production planning of biopharmaceutical manufacturing. *7th World Congress of Chemical Engineering 10-14 July, Glasgow. U.K.*

Lakhdar, K., Farid, S.S., Savery, J., Titchener-Hooker, N.J., Papageorgiou, L.G. **(2006)**. Medium term planning of biopharmaceutical manufacture under uncertainty, *PSE ESCAPE 2006, Garmisch-Partenkirchen, Germany.*