A SIMULATION-OPTIMIZATION APPROACH TO INTEGRATE PROCESS DESIGN AND PLANNING DECISIONS UNDER TECHNICAL AND MARKET UNCERTAINTIES

C. Marques[a], S. Moniz[b], J. Pinho de Sousa[a,b] and A. P. Barbosa-Póvoa[c]*
[a] Faculdade de Engenharia da Universidade do Porto, Rua Dr. Roberto Frias, Porto, Portugal
[b] INESC TEC, Rua Dr. Roberto Frias, Porto, Portugal
[c] Centro de Estudos de Gestão, Instituto Superior Técnico, Universidade de Lisboa, Av. Rovisco Pais, Lisboa, Portugal

Abstract

Technical and market uncertainties during product launch planning can have a significant impact in the companies decision-making process, particularly in today's business context of the pharmaceutical industry. This paper addresses this planning problem, considering both types of uncertainty and integrating process design and capacity decisions under limited resources. A Mixed Integer Linear Programing (MILP) model, with a two-step Monte Carlo Simulation (MCS) framework, is developed. The MCS component captures the simultaneous impact of uncertainty in product demand, in the outcomes of clinical trials, and in processing times, through respectively normal distributions, Bernoulli distributions, and uniform distributions. Results show that although the processing time variability is not relevant in the NPV, it inevitably affects the decision-making process by changing process design, scale up, and capacity extensions decisions. The proposed approach provides a robust and valuable information to support the medium and the long-term decisions associated with the product launch planning problem.

Keywords

Mixed Integer Linear Programing, Monte Carlo Simulation, Uncertainty.

Introduction

The pharmaceutical industry has been facing dramatically fast changes in the last decades, becoming more and more demanding and competitive. Not only the pressure by the regulatory agencies is always increasing, but also the strong competition from generics is forcing pharmaceutical companies to reduce prices and improve efficiency (Shah, 2004). On the other hand, the high dependence on patent effective life (Grabowski & Vernon, 2000), is clearly driving companies to provide faster medical drugs and compelling them to make decisions as earlier as possible, during the development stage. Therefore, time-to-market has been considered one of the most critical issues in this industry (Shah, 2004), and any delays associated with product approval can significantly jeopardize the company's ability to recover its investments. Moreover, not only the product, but also the production process needs to get a FDA approval so that the company can successfully launch the product into the market. This also means that any changes in the production process after this approval are not only costly, but also very time consuming. Thus, decisions concerning process design, production planning and capacity planning, are critical during new

* To whom all correspondence should be addressed, eq98022@fe.up.pt

drug development, and need to be taken as early as possible even when facing a highly uncertain environment (Moniz et al., 2015). In fact, uncertainty in product launch planning plays a very important role that cannot be neglected, as both technical and market uncertainties arise during product development. Process duration and clinical trials outcomes are some of the most relevant technical uncertainties, since they will directly affect the time-to-market of the new drug. On the other hand, market uncertainty mainly concerns the variability of product demand during clinical trials due to changes occurring, for example, in dose regimes (Farid et al., 2005) or in patient enrollment rate (Chen et al., 2012).

The product launch planning problem has been addressed in the literature mainly for portfolio management, and for capacity planning, although seldom considering the long-term process design decisions. Also, the integration of uncertainty into the models is still a complex and unsolved challenge. Verderame et al. (2010) presented a very interesting review of the key contributions in planning and scheduling optimization, with a special focus on uncertainty analysis. Two-stage stochastic programming is still the most widely used method to tackle uncertainty in process system engineering. Rotstein et al. (1999) addressed the capacity planning under clinical trial outcomes uncertainty, through a two-stage stochastic programming model that considers decisions such as product selection, capacity investment, allocation of manufacturing resources, and production plans. Many other authors have followed this trend. Rogers et al. (2002) developed a multistage stochastic program to address the optimal pharmaceutical research and development portfolio management. Decisions include the selection of the optimal product portfolio through a series of "continuation/abandonment options" for product development at each stage. Gatica et al. (2003) addressed the capacity planning problem under clinical trial outcomes uncertainty. In their work, a multistage stochastic programming formulation was also developed, considering scenario analysis to model the pass/fail uncertainty, but only for the last clinical trials phase. Decisions include the final product portfolio, capacity planning, and production planning. Levis and Papageorgiou (2004) also considered uncertainty in clinical trials outcomes to determine the product portfolio and to perform multi-site capacity planning. They proposed a two-stage, multi-scenario, mixed-integer linear programming model. More recently, Sundaramoorthy et al. (2012) proposed a multi-scenario, multi-period, mixed-integer linear programming formulation, considering uncertainty in the outcome of clinical trials for the product launch capacity planning, and developing an integrated framework based on continuous pharmaceutical manufacturing strategies.

Even if all these works are important contributions to this research domain, problems arise regarding formulation intractability when employing the two-stage stochastic programming, limiting their use, for example, to address several uncertain parameters simultaneously. In this context, there is therefore a clear need for innovative strategies in the decision-making process, exploring the effects of multiple sources of uncertainty in product launch planning.

Based on the authors' previous work (Marques et al., 2016), this study combines the developed MILP model with a two-step Monte Carlo simulation (MCS) framework, to tackle the uncertainties associated not only with the outcomes of the clinical trials and product demand, but also with processing times. The main contribution of this work is, therefore, the integration of long-term process design with medium-term production planning decisions, considering simultaneously several sources of uncertainty (clinical trials outcomes, processing times, and product demand).

Problem Definition

In this work, we consider a multipurpose batch plant for the primary production of two types of products: products under development and products already in commercialization. Thus, a limited amount of resources needs to be shared between the two production modes (campaign and short-term production) (Moniz et al., 2014). The product launch planning problem addressed in this study comprises the three clinical trials phases and ends with the regulatory approval of both the product and the production process, for a horizon of several years. The production plan is determined taking in consideration uncertainty in product demand, in processing times, and in the outcomes of clinical trials.

Lot traceability is also a critical issue in the pharmaceutical industry particularly during product development. In that sense, process design decisions such as lot-sizing and scale-up decisions are explicitly modelled in this work. The set of available lot-sizes for the starting raw materials is given. For the intermediaries, a Zero Wait (ZW) storage policy is considered, while, for the final products an Unlimited Intermediate Storage (UIS) is assumed, in order to cope with the product demand variability. However, for the products under development, the excess of final product at the end of each clinical trial cannot be reused and should be discarded. A penalty cost will be included in the objective function to take this aspect into account.

The product launch planning problem can then be formally defined as follows:

- Given: (i) a fixed time horizon discretized into equal periods; (ii) a set of products already in commercialization and under development; (iii) the recipes of each final product, including production yields; (iv) the set of processing units already installed in the plant and their maximum and minimum capacities; (v) the set of processing units available to add to the plant and their maximum and minimum capacities (vi) the task suitability for every processing unit; (vii) the lot sizes for each product; (viii) the probabilistic distributions for all the uncertain

parameters (product demand, clinical trial outcomes, and processing times); and (ix) all the operational and investment costs, as well as the sales prices for each final product.

- Determine the optimal product launch production plan, by defining: (i) the process to unit assignment; (ii) the timings and the sizes of scale-ups; (iii) the amounts to produce and store; and (iv) the capacity extensions required to accommodate the production of the under development products over the entire planning horizon.
- Maximize the Net Present Value (NPV) of the whole system operation.

Solution Approach

In this work a significant improvement is made to the previously developed methodology (Marques et al., 2016), in order to consider uncertainty in processing times. The conceptual framework integrating a Mixed Integer Linear Programming (MILP) model with the two-step Monte Carlo Simulation (MCS) previously developed will be briefly explained in this section.

Monte Carlo Simulation Framework

The MCS component of the approach captures the effect of uncertainty by randomly sampling a significant number of instances of each uncertainty parameter, based on their probabilistic distributions. Thus, to model variability in product demand and processing times, normal and uniform distributions respectively are considered for both types of products. On the other hand, to tackle the clinical trials pass/fail uncertainty for the products under development, Bernoulli distributions are considered due to the discrete, binary nature of the outcomes ("success" or "failure"). A MILP model is then solved for each of these instances.

A schematic representation of this framework is depicted in Figure 1 with the dark grey box highlighting the contribution of this work to the original framework.

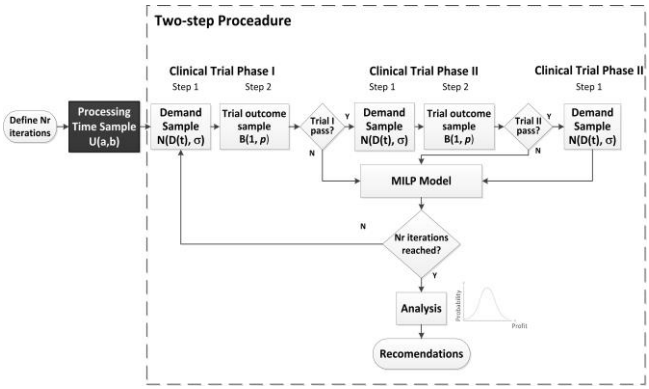


Figure 1. Monte Carlo simulation framework

In the case of products already in commercialization, a simple random sample is computed, in each iteration, for the processing time of each task, and for the product demand for each period. However, for the products under development, the product demand and samples of outcomes of the clinical trials are computed through a two-step procedure for each clinical trial phase (Figure 1). After defining the number of iterations, the random generation of the processing times is performed and then the first step is performed for the first clinical trial phase. In the first step, a random sample generation is executed for the product demand of each time period of the first clinical trial phase. At the end of this clinical trial phase, step 2 is executed with the random generation of a trial outcome (0="fail" or 1="pass"). A "pass" outcome means that this product will continue its development through the next clinical trial phase, and step 1 is performed again with a random generation of product demand for clinical trial phase II. The procedure is then repeated until the end of the planning period. On the other hand, if the outcome of the first trial is "fail", the two-step procedure stops and the MILP model will be run assuming that the product demand for the following periods is zero for that product (this meaning that the product will be abandoned, and that its development will not continue in the following trials).

At the end of this procedure the results are analyzed based on the obtained histograms and probability density functions.

MILP Model

The main goal of the model is to determine the optimal product launch production plan, considering the following key decision variables: (i) process/unit assignment binary variables; (ii) task batch-size continuous variables; (iii) number of batches defined through integer variables; (iv) number of lots of a given lot-size relative to the starting raw material defined by integer variables; (v) excess resource continuous variables; (vi) final product waste continuous variables only for the products under development; (vii) continuous variables for the deliveries at the end of each time period; and (viii) capacity extension integer variables. The model includes the following set of constraints:

- *lot-size constraints,* for the timing and sizes of scale-ups over the planning horizon;
- *excess resource balance constraints,* to determine the material availability over time for all materials (raw materials, intermediaries, and final products);
- *resource capacity constraints,* to bound the material availability between minimum and maximum values;
- *demand constraints* imposing production requirements;
- *batch size constraints,* to ensure that the total amount processed is bounded by the processing units capacity;
- *production capacity constraints* (the time available for each processing unit and period, including capacity extensions), with a distinction between products in commercialization and products under development, since the model only allows capacity extensions for the under development products. This distinction is necessary in order to minimize undesirable changes in

the already approved production process of the products in commercialization;

- *process design constraints,* to ensure process stability over the planning horizon.

The objective function (see Eq. (1)) is the maximization of the NPV resulting from the income of product sales (*INCO*) minus operational costs (OC), storage costs (SC), disposal costs associated with the unused final products under development (WC), changeover costs (COC), scale-up costs (LC), and investment costs (IC).

$$\max NPV = INCO - OC - SC - WC - COC - LC - IC \qquad (1)$$

Computational Results and Discussion

Illustrative Example

A planning horizon of 5 years discretized in 10 periods of equal duration (6 months), and a set of 5 products (3 under development, and 2 already in commercialization) are considered in this example. The product demand forecast profiles are known for each product (see Figure 2).

Figure 2. Demand forecast profile for products under development (PA, PB, and PC) and for products in commercialization (PD and PE)

All the products considered follow a similar production recipe, as presented in Figure 3. This recipe comprises three aggregated tasks (reaction, filtration, and drying), and for each task, three types of processing units are already available in the plant, according to the characteristics presented in Table 1.

Capacity extensions are modeled considering the acquisition of additional processing units among each one of the equipment types defined in Table 1.

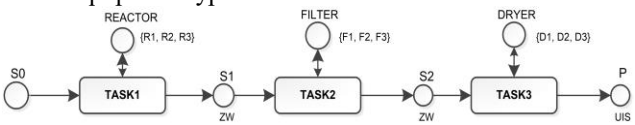
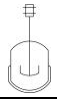


Figure 3. Recipe followed by the products

Uncertainty is modeled considering normal distributions for the product demand, with a standard deviation of 30% for products under development, and 10% for products in commercialization (values derived from the forecasts in Figure 2). For the processing times, uniform distributions are considered. A symmetric deviation of ± 33% around the average was assumed for this random variable, for both types of products. For the clinical trials outcomes, Bernoulli distributions are used considering the given probabilities of success, for each product and clinical trial phase.

Table 1. Main characteristics of the processing units

	Unit code	Max. cap. (kg)	Min cap. (kg)	Inv. cost (rmu)
Reactors 	R1	500	5	20,000.00
	R2	1500	15	35,000.00
	R3	4500	45	70,000.00
Filters 	F1	500	5	18,000.00
	F2	1000	10	35,000.00
	F3	3000	30	50,500.00
Dryers 	D1	300	3	18,000.00
	D2	800	8	35,000.00
	D3	2000	20	50,500.00

Results

The MILP model and the MCS component were implemented using IBM ILOG CPLEX Optimization studio, version 12.6.0, and the results were obtained running the MCS framework (Figure 1) for 1000 iterations. The results (objective function and decisions variables) are presented as histograms and probabilistic distributions.

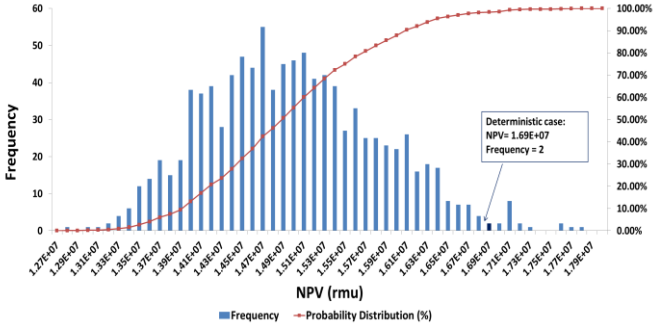


Figure 4. NPV histogram and probability distribution

Figure 4 shows the values obtained for the NPV, with the maximum value for the NPV observed under uncertainty being 1.78 x 10^7 relative monetary units (rmu), with a minimum value of 1.27 x 10^7 rmu, and an average of 1.49 x 10^7 rmu. These values are very similar (slightly lower) to those obtained without considering uncertainty in

processing times. Not only the NPV values, but also the slightly skewed right pattern of the histograms are identical (the differences are less than 1%).

This result is natural, since the major impact of uncertainty comes from the clinical trials "pass"/"fail" variability, leading to a further development of the product until its commercialization or to its abandonment, with the loss of all the investments made so far. Therefore, the effect of the additional uncertainty in processing times is almost unnoticed in the NPV values.

Nevertheless, regarding the process design, scale-up, and capacity extensions decisions, some relevant differences arise when considering the uncertainty in the processing times. Concerning the process design and scale-up results, the main difference occurs in the last periods of the planning horizon, with the selection of processing units with higher capacities in almost all the products considered. These results are particularly evident for the PC product (under development). We therefore briefly describe this case here.

Figure 5 and Figure 6 present the most frequently selected set of processing units associated with lot-sizes (with and without additional uncertainty in processing times). In order to make the results more reliable a "robustness" measure was defined - the percentage of occurrences of each process design in more than two periods in the same iteration.

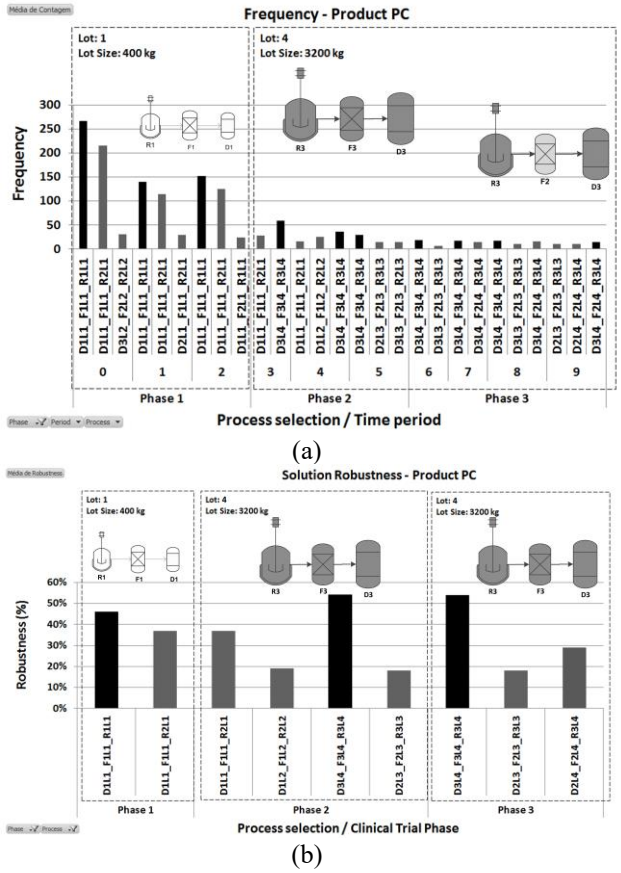


Figure 5. Results for product PC (under development), with uncertainty in processing times: (a) process design selection;(b) solution robustness

From the analysis of these two figures, we can state that, when considering uncertainty in processing times (Figure 5), scale-ups tend to occur earlier and associated with processing units of higher capacity. In this case, for example, a scale-up occurs from phase I to phase II, and for the clinical trial phase II the most frequent, and robust process design configuration is for lot-size 4 (3200 kg) and processing units R3_F3_D3.

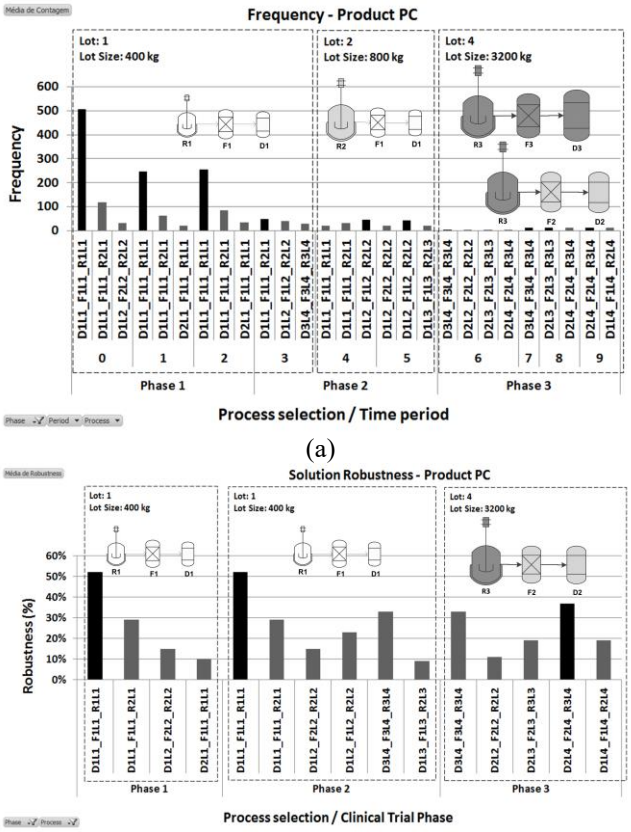


Figure 6. Results for product PC (under development), without uncertainty in processing times: (a) process design selection; (b) solution robustness

When not considering uncertainty in processing times, the combined analysis of frequency and robustness leads to the selection of lot-size 1 (400 kg) and processing units R1_F1_D1. In this case, the scale-up will only occur from phase II to phase III. These results do therefore provide interesting information on the risks of the decision-making process if not all relevant uncertain parameters are taken into account.

Finally, concerning the capacity extension, there are also some differences. Although the overall observed capacity extensions for both cases are not significant (see Figure 7), when introducing uncertainty in processing times this has a significant increase of about 56% on average. The results obtained for the two situations are compared in Figure 7 (these are average values for the 1000 iterations).

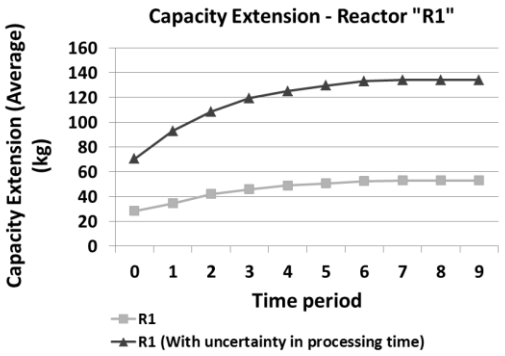


Figure 7. Capacity extension for reactor R1, with and without uncertainty in processing time

Conclusion

This paper focus on the effects of simultaneously considering several sources of uncertainty in the product launch planning problem. A previously developed approach (Marques et al., 2016), that integrates a MILP model with a two-step Monte Carlo Simulation framework, has been improved in order to capture uncertainty in product demand, in the outcomes of clinical trials, and in processing times. The results obtained with this new approach provide valuable information to support the medium and the long-term decisions associated with the problem, by efficiently assessing the joint impact of several sources of uncertainty. It is clear from the results that uncertainty in processing times is not negligible, even in situations where other types of uncertainty are present. Although, the impact of the processing time variability in the NPV is not significant, the results show that it will inevitably affect the decision-making process, by changing the best strategies in what concerns process design configuration, and times and sizes of scale-ups.

Future research will include a better systematization of the whole decision-making process, in order to go beyond a purely economic dimension, and to also integrate key sustainability aspects. Also, the scalability of the model to solve more complex and large instances should be addressed in further research.

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