Title: A simulation-optimization approach to integrate process design and planning decisions under technical and market uncertainties: a case from the chemical-pharmaceutical industry

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Highlights

A novel approach, combining a mixed integer linear programming (MILP) model with a two-step Monte Carlo simulation (MCS), to specifically address technical and market uncertainties during new product development, in the pharmaceutical industry

- Integration of strategic (process design and capacity extensions) and tactical (quantities to produce and store) decisions, simultaneously considering: a) the resources limitations associated to the need of processing, in the same plant, products under development and products in commercialization; and b) lots traceability.
- This new approach has proven to be effective in capturing the effects of uncertainty in process design and scale-up decisions, as well as in capacity and production planning decisions, during product-launch planning.
- Results clearly show the inherent risks associated to decisions taken under deterministic scenarios, and the gains associated to a large-range analysis of the uncertainty parameters, such as the access to valuable information early enough, for a sound long-term decision making process.

A simulation-optimization approach to integrate process design and planning decisions under technical and market uncertainties: a case from the chemical-pharmaceutical industry

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Abstract

This study addresses the product-launch planning problem in the chemical-pharmaceutical industry under technical and market uncertainties, and considering resource limitations associated to the need of processing in the same plant products under development and products in commercialization. A novel approach is developed by combining a mixed integer linear programming (MILP) model and a Monte Carlo simulation (MCS) procedure, to deal with the integrated process design and production planning decisions during the New Product Development (NPD) phase. The Monte Carlo simulation framework was designed as a two-step sampling procedure based on Bernoulli and Normal distributions. Results show the unquestionable influence of the uncertainty parameters on the decision variables and objective function, thus highlighting the inherent risks associated to the deterministic models. Process designs and scale-ups that maximize expected profit were determined, providing a valuable knowledge frame to support the long-term decision-making process, and enabling earlier and better decisions during NPD.

Keywords: Process design; Capacity planning; Scale-ups; Mixed Integer Linear Programing; Monte Carlo simulation; Uncertainty.

1. Introduction

1.1. Motivation

The pharmaceutical industry operates in a very dynamic, highly regulated and competitive business context, being one of the most important manufacturing sectors in Europe (EFPIA, 2016). The specificities of this industry are well known in the Process System Engineering (PSE) community. The heavy regulatory burden, high investment in R&D with very low success rates, and long periods for new product launch, clearly differentiate this industry from other sectors and impose significant managing challenges (Laínez et

al., 2012). Furthermore, the liberalization of the global pharmaceutical market and the pressures of the regulatory agencies for a price reduction in medical drugs has paved the way to generic competition (Federsel, 2006). Considering the fact that the costs of imitation are extremely low when compared to the costs of innovation in pharmaceuticals, generic competition is becoming increasingly fierce, particularly regarding economic issues (Grabowski & Vernon, 2000). In that sense, this industry is now highly dependent on patent effective life, being forced to deliver medical drugs faster and more efficiently. As stated by Shah (2004) and more recently by (Samuel Moniz et al., 2015b), it is clear that *time-to-market* is the most critical issue in this industry, and that any delay associated with the product launch process entails a significant loss in future profits. This demanding business context has encouraged companies to invest in production capacity and to make process design decisions as early as possible, even before knowing if the products will ever reach the market (Kaminsky & Yuen, 2014). Those decisions are thus highly risky, involving several sources of uncertainty that must be considered during the decision-making process (Samuel Moniz et al., 2015a).

In addition to the economic dimension of these decisions, sustainability concerns are also one main motivation of this work. In recent years a paradigm shift has been observed, with sustainability aspects being considered simultaneously with economic goals (Bakshi & Fiksel, 2003; Barbosa-Póvoa, 2012) Efficient resource utilization is becoming a global challenge, clearly reflected in the recent SPIRE (Sustainable Process Industry through Resource and Energy Efficiency) initiative, where the main goals towards improved efficiency and competitiveness are fully aligned with the European Horizon 2020 agenda (EC, 2013). The fine chemical and pharmaceutical industry plays an important role in this regard due to their high dependence on resources such as: water, raw materials and energy (Halim & Srinivasan, 2008, 2011; Wernet et al., 2010). Thus, implementing efficient production planning decisions will definitely contribute to better resource utilization and waste minimization. More than ever, the need to achieve higher efficiency and cost savings in resource utilization, combined with the urgency in reducing the *time-to-market* of under development pharmaceutical products, clearly justifies further research in more advanced and reliable methods to solve real world planning optimization problems under uncertainty.

Accordingly, the work presented in this paper addresses the product-launch planning problem, considering uncertainty on the demand and on the pass/fail outcomes of clinical trials. This work integrates process design and planning decisions, considering the resource limitations in processing, in the same plant, products under development and products already in commercialization. In practice, this approach provides contributions to enhance decision-making processes, with four overall goals: (i) maximize the profit of companies; (ii) minimize investments; (iii) minimize future changes in the production process; and (iv) improve processes efficiency, particularly in what concerns resource utilization and waste reduction.

Therefore, improving the balance between available resources and product demand, while achieving interesting and sustainable results, is one of the main goals of the decision-making framework proposed here. The majority of currently available approaches are supported by deterministic models based on the maximization of expected values, without considering the highly stochastic nature of the problems (Li & Ierapetritou, 2008; Verderame et al., 2010). In this work, we have developed a MILP model for optimal product-launch planning, combined with a two-step MCS framework, to tackle the types of uncertainty referred above (demand and clinical trials pass/fail).

1.2. Pharmaceutical Product Launch

1.2.1. New Product Development (NPD)

The development of new drugs is an expensive and time-consuming process that comprises several consecutive steps, such as: discovery, pre-clinical tests, clinical trials, regulatory approval and market launch (Chen et al., 2012; Colvin & Maravelias, 2008). Figure 1 depicts the pharmaceutical product lifecycle, since discovery to manufacturing and distribution. According to Laínez et al. (2012), the time from discovery to market launch can take up to 15 years, and the average cost of a new drug is about US$ 1.3 to 2 billion, with about 50% representing clinical trial costs.

Clinical trials involve a series of very rigorous tests conducted on human beings, to assess the safety, efficacy and dosage levels of the new compound. These trials comprise three successive phases (I, II and III). In phase I, the new molecular entity is tested in 20/100 healthy volunteers, for safety assessment. In

phase II, 100/500 volunteer patients are tested, to ensure the efficacy of the compound. Phase III usually involves thousands of volunteer patients, with the main purpose of comparing the performance of the new treatment with other existing treatments, and assessing its long-term effects (Colvin & Maravelias, 2008; Levis & Papageorgiou, 2004). The clinical trials process may take approximately 5 to 6 years (Colvin & Maravelias, 2008) and only after its successful completion and the FDA approval, the new compound is able to be commercially launched. In that sense, decisions such as "how much to produce?", "when to produce?" and "with what resources?", during the new product development process, are critical, and will have a significant impact on the company's sustainability. As failing a trial dosage can seriously compromise the *time-to-market* of the new drug, all the necessary resources need to be available as soon as they are needed (Levis & Papageorgiou, 2004). These decisions are, therefore, taken under significant levels of uncertainty, particularly regarding product demand. The high variability of product demand during clinical trials results mainly from the uncertainty of the pass/fail outcomes of clinical trials and is partially due to patient drop out during the progress of treatments (Chen et al., 2012). On the other hand, if the compound fails at any clinical trial phase, the whole investment made until then is considered lost. This makes the NPD (New Product Development) stage one of the most critical in the whole product life cycle.

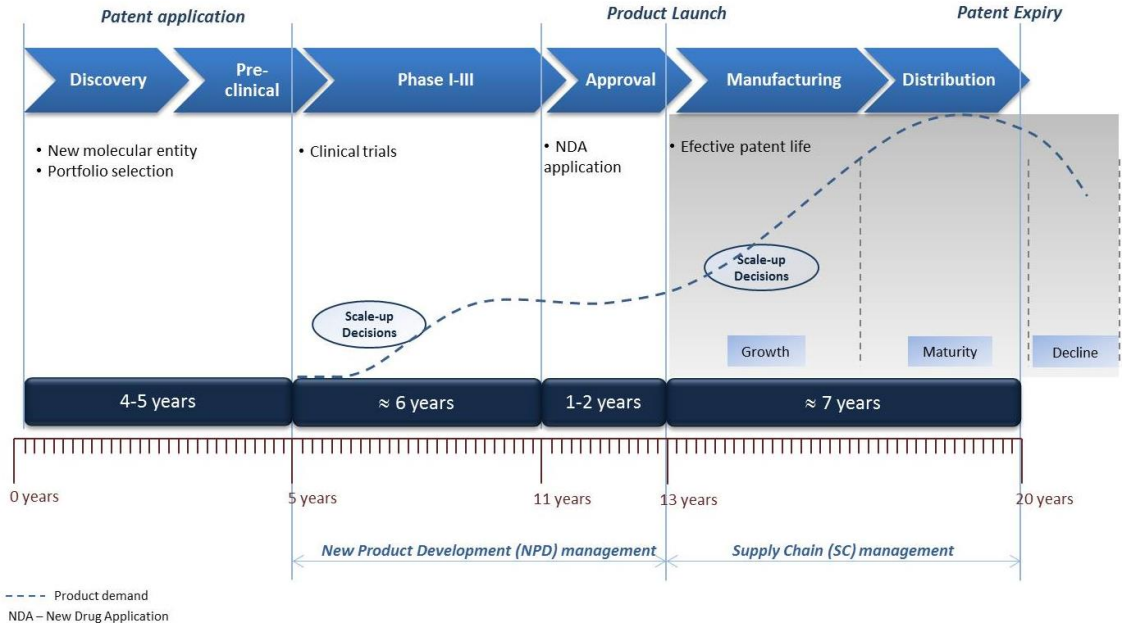


Figure 1. Pharmaceutical product lifecycle.

1.2.2. Process design

Along with the product development, also the production process for the new drug needs to be developed, in order to get the final approval by the regulatory agencies. Moreover, the company itself must also guarantee that it will be able to routinely manufacture reproducible batches of the new drug (Colvin & Maravelias, 2008). Traditionally, the pharmaceutical industry operates in batch and multipurpose production systems, simultaneously processing campaign and short-term modes (Samuel Moniz, Barbosa-Póvoa, et al., 2014) . In these plants, products already in commercialization and products under development compete for the same resources. In that sense, providing the right amount of resources, at the right moment, to each trial, represents a key management challenge, with the development of the production process playing a very critical role (Samuel Moniz et al., 2015a). The company starts by providing small amounts of the new product to the early stages of the clinical trials. Then it up-scales the process as needed to fulfill the last stages of product development and, finally, it has to guarantee the satisfaction of commercial demand, in terms of quantity and quality (Stonebraker, 2002). Process design and capacity decisions are therefore of paramount importance, and late-stage process changes will inevitably compromise the market launch of the new drug (Federsel, 2003).

Since changing the process after this being approved is very costly and complex, any poor decision taken during the early stages will have a huge impact in the commercialization phase. According to Federsel (2003), the process should be frozen no later than clinical trial phase II, in order to guarantee a drug production of good quality for long-term toxicology and stability testing. Therefore, in practice, these decisions are made with two conflicting objectives: (i) they should be sound and based on a considerable amount of information; and (ii) they should be made early enough to prevent any delays in the completion of the trials. According to Stonebraker (2002), the capital investments for the production facility usually occur around five years before the market launch of the new drug. As late decisions could significantly jeopardize the future incomes of the company, process design and capacity decisions, such as the assignment of processes to units, scale-up, and the acquisition of production units, have to be made under a significant uncertainty context.

2. Background

New product development management in the pharmaceutical industry has been one of the major concerns of the process system engineering community in recent years. In this area, the great majority of published works focus on product portfolio selection, on capacity planning, and on supply chain management during clinical trials (Laínez et al., 2012).

Typically, planning decisions are formulated as deterministic optimization problems in which all the parameters are assumed to be known. However, the importance of incorporating uncertainty into planning and scheduling models is increasingly recognized by the academic community (see some interesting, recent review articles such as Li and Ierapetritou (2008); Sahinidis (2004); Verderame et al. (2010)). Verderame et al. (2010) present a comprehensive overview of the main contributions in planning and scheduling optimization under uncertainty, across multiple industrial sectors The most commonly used approach for planning under uncertainty is two-stage Stochastic Programming (SP) (Steimel & Engell, 2015). Planning decisions are typically taken in two stages, where strategic decisions ("here and now") are made in the first stage under significant uncertainty, and operational decisions ("wait and see") are made in a second stage after the resolution of the uncertainty. Usually, uncertainties are modelled as a set of discrete scenarios, as a way to account for all possible future outcomes, and each scenario is solved as a deterministic problem.

Rotstein et al. (1999) was one of the first papers addressing capacity planning under uncertainty in the outcomes of clinical trials. They developed a two-stage SP approach, with the first stage dealing with decisions such as product selection, initial capacity investment, and initial allocation of manufacturing resources to products. In a second stage, decisions are made after the completion of the clinical trials, and they include: additional capacity investments, re-allocation of manufacturing resources to products, and production plans. Papageorgiou et al. (2001) developed a MILP model to simultaneously address the selection of a product development and introduction strategy, and a long-term capacity planning and investment strategy, at multiple sites. However, this work does not account for the uncertainty associated to product demand or the outcomes of clinical trials. At the same time, Maravelias and Grossmann (2001) addressed the problem of simultaneously planning the new product development and the design of batch manufacturing facilities. The authors proposed a multi-period MILP model that maximizes the expected net present value of multiple projects (products under development). A two-stage stochastic optimization approach is adopted to account for the uncertainty in the outcome of the trials.

Gupta and Maranas (2000) also propose a two-stage SP approach, to address the multisite midterm supply-chain planning problem under demand uncertainty. The production decisions are made "here-and-now", and the supply chain (inventory and distribution) decisions are postponed as "wait-and-see". Later, the same authors (Rogers et al., 2002) presented a real-options strategy to determine the optimal product selection decisions in the pharmaceutical R&D portfolio management.

Gatica et al. (2003b) presented a multistage programming formulation for capacity planning with uncertainty associated to the outcomes of clinical trials. A scenario analysis was performed, and these uncertainty issues were modelled via a tree of scenarios. However, in this work only the outcomes of the last phase of clinical trials were considered, and this may obviously lead to suboptimal solutions. The same authors later presented (Gatica et al., 2003a) a scenario aggregation–disaggregation approach, with scenarios being grouped into predetermined clusters, based on a mapping procedure between products and

the outcomes of clinical trials. Cheng et al. (2003) addressed the problem of designing and planning under market and technological uncertainty. The decision process explicitly incorporates both the upper-level investment decisions and the lower-level production decisions, as a two-stage optimization problem, with a multi-objective Markov chain. Later, Levis and Papageorgiou (2004) also proposed a two-stage, multi-scenario MILP model, to determine the product portfolio and to perform the multi-site capacity planning, considering uncertainty in the outcomes of clinical trials. In the same year (Sundaramoorthy & Karimi, 2004) presented a multi-period, continuous-time MILP model to address the supply chain management problem in a pharmaceutical plant considering new product introductions (active ingredients or intermediates) and outsourcing. The model determines the production and inventory levels, and the level of outsourcing for existing intermediates to maximize gross profit. However, this work does not account for uncertainty, and it is assumed that the scale-up procedures are completed before the new product enters the facility for commercial production. A scenario-based multi-stage Stochastic Programming model was developed by Colvin and Maravelias (2008) for planning the clinical trials in the pharmaceutical R&D pipeline. The model determines which trials should be performed in each planning period, taking into account the uncertainty in the outcomes of the clinical trials. The authors use a reduced set of scenarios to limit the size of the problem. Later, they extend their work (Colvin & Maravelias, 2009) to simultaneously address the scheduling of clinical trials and resource planning. More recently, the same authors (Colvin & Maravelias, 2011) developed a multi-stage SP framework for R&D pipeline management, accounting for interdependencies between projects and tasks, and incorporating risk management considerations (both value-at-risk and conditional value-at-risk novel formulations). The main goal of this approach is to determine the schedule of tasks and make the resource planning decisions that maximize the Expected Net Present Value.

Lakhdar et al. (2006) presented another two-stage SP, by developing a MILP model based on Chance Constrained Programming (CCP), for medium-term planning of biopharmaceutical manufacturing with uncertainty on the fermentation titers. Later, Lakhdar and Papageorgiou (2008) presented a two-stage, multi-scenario MILP model for optimizing production plans in a biopharmaceutical manufacturing facility, addressing the same technical uncertainty. And more recently, Sundaramoorthy et al. (2012), developed a framework for capacity planning, ensuring the availability of enough resources for the foreseen product demand (a multi-scenario, multi-period MILP formulation, that takes into account uncertainty in the outcomes of clinical trials).

Although two stage stochastic programming approaches are still the most widely used, with some interesting results having been achieved in recent works, these procedures have important drawbacks that limit their full application. The need to generate a large number of scenarios significantly increases the model size, leading to formulations that are computationally intractable. Moreover, decisions such as how many scenarios to generate and which scenarios to generate are neither simple nor obvious, and the analysis of each scenario can be a very complex and time consuming task. The inevitable increase in the number of scenarios, with the number of products and outcomes of the clinical trials, makes in fact this methodology less attractive to tackle many real problems.

Nevertheless, an interesting body of literature dedicated to *simulation-optimization* based approaches has emerged in the past years, to tackle some of the problems arising in new product development management. Subramanian et al. (2001) developed an approach (the “SIM-OPT” architecture) to address the R&D pipeline management problem. The approach combines mathematical programming and discrete event system simulation, to tackle uncertainty and control the underlying risk. The concept of time lines is introduced to accommodate various stochastic realizations present in the R&D pipeline. Later, the same authors (Subramanian et al., 2003) extend their previous work to include methods for improvement of the stochastic optimization problem solution. (Jung et al., 2004) adopted part of the “SIM-OPT” architecture previously developed (Subramanian et al., 2001) to determine the safety stock levels under demand uncertainty in a chemical process industry supply chain. They have later extended their work to determine the safety stock levels in a multi-stage supply chain (Jung et al., 2008). Blau et al. (2004) also addressed the product portfolio selection in the pharmaceutical industry, considering project uncertainties and dependencies. The developed approach combines a discrete event simulation with a genetic algorithm to select the optimal sequence of projects that maximizes the expected economic returns. (Choi et al., 2004)

addressed the stochastic Resource-Constrained Project Scheduling Problem (RCPSP) using a discrete-time Markov chain for modeling uncertainties in task duration, cost and task results. A dynamic programing formulation, in a heuristically confined state space, was developed to solve the problem. (Rajapakse et al., 2005) developed a decision-making tool based on discrete event simulation to predict process and business outcomes of the biopharmaceutical drug development process. Wan et al. (2006) developed a simulation based optimization approach to address multi-stage capacity expansion problems for risk management in the pharmaceutical product pipeline. (Varma et al., 2008) also developed a computational framework (SIM-OPT), based on a combination of discrete event simulation and mixed integer programming, to address the joint optimization of scheduling and resource allocation decisions in the context of pharmaceutical R&D pipelines. More recently, Perez-Escobedo et al. (2012) developed a simulation-optimization approach combining a multi-objective Genetic Algorithm optimization framework coupled with a discrete event simulator to address the portfolio management and scheduling of new drugs in the pharmaceutical industry. In the same year, Chen et al. (2012) addressed the clinical trial supply chain management problem, with a simulation-optimization framework that combines patient demand simulation, stochastic demand forecasting, a mathematical programming to optimize the production and distribution cost, and discrete event simulation to capture uncertainties.

Notwithstanding the important contributions of the above papers, most of the simulation-optimization approaches have been developed to address the R&D pipeline management and resource allocation (including portfolio selection and task scheduling decisions) and not the process design and production planning decisions at facility level (as addressed in this work). Moreover, the effect of resource sharing due to processing in the same plant products under development and products in commercialization, as well as the long-term capacity investment decisions (including scale-up analysis), are seldom considered in these works.

It seems clear that there is an evident scarcity of research in sound alternatives to the two-stage SP for simultaneously addressing process design and planning decisions, under market and technical uncertainties. An alternative seems to be MCS (as proposed in this work), used to determine the impact of the uncertainty parameters, through the estimation of their probability distributions. Bassett et al. (1997) developed a framework for including uncertainty parameters into a general aggregate production planning procedure, or resource constrained scheduling problems, using MCS. The framework does not determine a specific schedule, but instead it determines robust operating policies that support the decision-making process. Farid et al. (2005) also used MCS to model technical and market uncertainties of biopharmaceutical batch manufacturing processes, based on a hierarchical framework. More recently, Eberle et al. (2014) proposed a framework for measuring and improving the production lead time of pharmaceutical processes, with MCS being applied to predict future total lead time based on probabilistic distributions. At the same time, Kaminsky and Yuen (2014) developed a model to address the problem of capacity investments during clinical trials, using a Bernoulli process with unknown rate. Through this model, the company re-evaluates its capacity investment strategy, as information about the potential success of the product is continually updated via the results of the clinical trials.

In the current work, an extended version of the authors previously developed MCS framework (Marques et al., 2016) will be explored and enhanced, by incorporating some specific features of the pharmaceutical industry, such as lot traceability, scale-up and process design decisions, and clinical trials waste management. The proposed framework allows a deep investigation of a large number of possible values for the uncertainty parameters (instead of just scenarios), and provides a comprehensive analysis and assessment of the risks associated with these parameters.

3. Problem Statement

In order to increase economies, pharmaceutical production plants typically operate in batch and multi-purpose production systems, simultaneously processing, in the same plant, commercial and pilot scale (under development) products. In this production mode, a great variety of products can be produced by sharing all available resources (including processing units, raw materials, intermediaries, and utilities) with the same or different sequences of operations (Floudas and Lin (2004), Barbosa-Póvoa (2007)). Even if

continuous manufacturing is currently a developing and promising area in the pharmaceutical industry, batch operating modes still prevail in this industrial sector (see Lee et al. (2015)).

We will therefore assume that, to adequately meet the demand requirements, plant resources are shared between these two types of products, with capacity expansions expected to accommodate this simultaneous production. Nevertheless, capacity expansions for the products in commercialization are, in general, highly undesirable. Not only because of the high costs involved in changing a production process that has already gained regulatory approval, but also because of the time consuming procedure of revalidating the process, whenever a modification is made. Therefore, the model developed in this work will only allow capacity increases associated to the products under development.

The product development process considered here encompasses the three clinical trials phases, and ends with the regulatory approval (of both product and production process) and the product launch.

In a typical pharmaceutical company, the development phase comprises a portfolio of products that are in different stages of development (different clinical trial phases), at any given time. Although the proposed model could be easily adapted for this situation, for the sake of clearness we will assume that a known set of products reaches phase I of the clinical trials at the same time, and that the optimal production plan is determined considering the probabilities of success of each product, at each phase of the clinical trials.

To accommodate all phases of the clinical trials, a planning horizon with several years is divided into equal time intervals ($t \in \mathbf{H}$). Due to the long time horizon imposed by clinical trials, demand uncertainty is considered for both types of products. For the products under development, uncertainty arises from two main sources: (i) outcomes of the clinical trials (pass/fail outcomes); and (ii) demand variability mainly due to patient drop out during the trials progress.

Moreover, *lot traceability* is also modelled in this work, due to its importance for the pharmaceutical industry. Nevertheless, a distinction should be made between *lots* and *task-batches*. According to S. Moniz et al. (2013), the term "lot" refers to the total amount (quantity) of stable intermediary or final product that is produced following the known recipe (that includes the set of tasks, processing units, and materials). On the other hand, "task-batches" are limited by the capacity of the processing units and correspond to the amount of material produced by each task (tasks are elements of the production process of a lot). Thus, in order to ensure *lot traceability*, lots are associated to all materials, including raw materials, intermediaries and final products. In this work, lots are defined by the starting raw materials, with the availability of these materials being limited by predetermined lot-sizes. The model will select some of these lot-sizes in order to achieve the best trade-off between those sizes and the operational costs associated to the capacities of the processing units needed to process them.

In terms of storage policies, it is assumed that in each period, storage is only allowed for the final products in order to accommodate the demand variability. For the products under development, the excess of final product at the end of each clinical trial phase must be considered as wastage and discarded, since it cannot be reused. Thus, a critical balance between the amounts required for the trial and the additional costs associated with the leftovers at the end of each clinical trial, should be achieved by the model.

Regarding the production yields, a distinction between the two types of products is also made. For those under development, lower levels of production yields are considered due to their still premature manufacturing process when compared with the products already in commercialization.

The main goal of this planning process is to determine the "optimal" production plan, the process design, and production scale-ups for a set of products ($p \in P$), ensuring that all demand requirements are fulfilled. Because failures in the deliveries to the trials seriously compromise the time-to-market and the payback of the investments, we assume that all the demand requirements will be fulfilled for the under development products. Therefore, the problem addressed in this work is formally defined as follows.

Given:

(i) a fixed time horizon, discretized into several time periods of equal duration ($t \in \mathbf{H}$);
(ii) a set of under development products entering clinical trials ($\mathrm{p} \in \mathbf{P}^{\mathrm{U}}$);
(iii) a set of products already in commercialization ($p \in \mathbf{P}^{\mathrm{C}}$);
(iv) the recipes of each final product ($p \in \mathbf{P}$);
(v) the lot sizes available for the raw materials of each product ($m \in \mathbf{W}_p$);
(vi) the set of processing units initially installed in the plant ($e \in \mathbf{E}$);
(vii) the maximum and minimum capacities of each processing unit;
(viii) the task suitability for every processing unit and the respective processing times;

(ix) the probabilistic distributions of the product demand;
(x) the probabilities of success of the under development products in each clinical trial phase;
all the operational and investment costs associated to each task and processing unit, as well as the sales prices of each product;

the key decisions for the product launch production planning problem are:

(i) best set of processing unit types for each process;
(ii) size and timings of scale-ups;
(iii) amount (quantity) to produce in each time period;
(iv) how much to store in each time period;
capacity extension requirements for the under development products;

in order to maximize the Net Present Value (NPV) of the company operations related to these projects.

4. Proposed Method

4.1. A two-step MCS framework

The conceptual framework developed in this work integrates a MILP model with a two-step MCS. The MCS component randomly samples a large number of instances of product demand and outcomes of the clinical trials, until a stopping criterion is met. For each of these instances, the MILP model is solved and an optimal solution is obtained. The uncertainty parameters are randomly sampled from their given probabilistic distributions. Since normal distributions have been often used to capture the essential characteristics of product demand uncertainty (Wellons and Reklaitis (1989), Petkov and Maranas (1997), Gupta and Maranas (2003)), the *normality* assumption is also considered in this work. On the other hand, to model the uncertainty associated with the outcomes of the clinical trials, the probability of success of each product, at the end of the trial phases, is given by Bernoulli distributions, since there are only two possible results of the clinical tests: "success" or "failure".

For the products already in commercialization, only the demand is randomly sampled, but for those under development both uncertainty parameters (product demand and clinical trial outcomes) are randomly generated, in a two-step procedure performed for each clinical trial phase (see Figure 2). The random sampling for the product demand (step 1) is performed for each time period, while the sampling for the outcomes of the clinical trials (step 2) is performed only at the end of each clinical trial phase, as illustrated in the detailed diagram of Figure 3 (note that the procedure starts with the definition of the number of iterations to be performed).

In step 2, if the outcome of the clinical trial test is "pass", step 1 is performed again with the random generation of a value for the product demand for the next clinical trial phase, and so on. However, if the outcome is "fail", the two-step procedure stops (step 1 of the next trial phase will not be performed) and the MILP model will be run considering that the demand for that product is zero for the following periods (this meaning that the development of this product will be abandoned). This procedure is executed for all products in each MCS iteration, and the MILP model is run considering the product demands obtained by this procedure.

At the end of the MCS procedure, we get the probability density function for the objective function, and the results for the probabilistic occurrence of the decision variables can be derived. These results are then analysed to support decision-making concerning the process design configuration, as well as the capacity and planning decisions during product development.

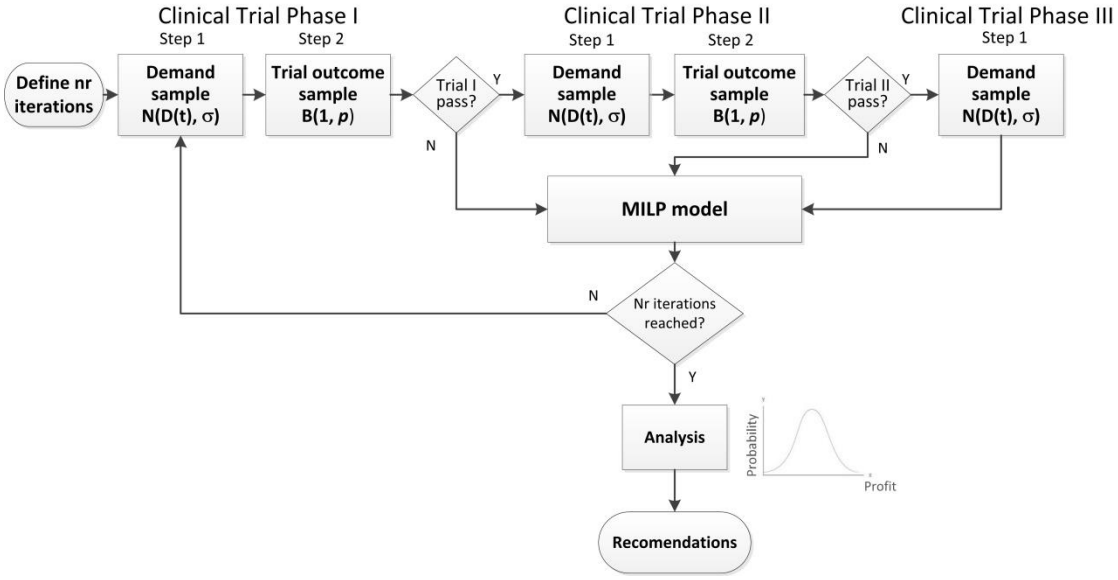


Figure 2. Schematic representation of the two-step MCS framework.

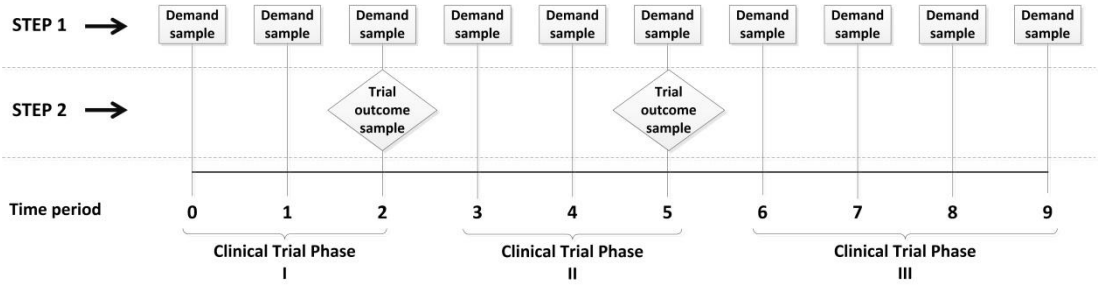


Figure 3. The two-step MCS procedure.

5. MILP Model

The optimal plan will be determined considering that resources are shared among the production of products under development and the production of products already in commercialization, over a planning horizon of several years. Thus, detailed time and task-sequencing constraints will not be considered in this model. All material requirements, as well as all storage levels and production yields, will be precisely defined through the model parameters and decision variables.

The process design configuration and planning decisions are represented by the following decision variables:

- the *process/unit assignment* binary variables Y_{plet}, that are equal to 1 if product *p* of lot *l* is assigned to processing unit *e* in period *t*;
- the *task batch-size decisions* are associated to continuous variables B_{klt}, denoting the amount to be produced by each task *k* and lot *l* at period *t*;
- the *number of instances of each task k* of lot *l* are defined through the integer variables N_{klt} for each period *t*;
- the *lot-size decisions* are modelled by integer variables L_{mlt}, that define the number of lots of each lot-size *l* from a set of pre-determined lot sizes, for the starting raw material $m \in \mathbf{W}_p$ at each period *t*;
- the *excess resource* continuous variables R_{mlt}, that define the total amount available of material *m* of lot *l* at each period *t*;

- the *final product waste* continuous variables $W_{ml}|_{t=t_i^F}$, that denote the leftovers of the under development final products *m* ($m \in \mathbf{P^U}$) at the end of each clinical trial *i* (the final product that was not used during the clinical trial *i* and must be destroyed since it cannot be reused);
- *deliveries* are given by the continuous variables D_{mlt}, denoting the total amount of material *m* (final product) of lot *l* delivered at period *t*;
- the *unused capacity* continuous variables F_e, that define the amount of capacity not used by product *p* (products in commercialization) in processing unit *e*, and that will be available for the production of under development products;
- the *capacity extension* integer variables A_{et}, that define the number of additional processing units *e* to be added to the plant at period *t*.

The complete formulation encompasses constraints (1) to (15) and the objective function (16), as presented in the next section.

5.1. Mathematical formulation

NOTATION

Indices

e	Processing unit
i	Clinical trial phase
k	Processing task
l	Lot
m	Material (may be a raw material, an intermediary or a final product)
p	Final product
t	Period

Sets

E	Processing units
$\mathbf{E}_p$	Processing units associated with product *p*
$\mathbf{E}_m$	Processing units associated with raw material $m \in \mathbf{W}$
H	Planning horizon
$\mathbf{H}_i$	Time interval of the clinical trial phase *i*: $H_i = \{t_i^{initial}, \ldots, t_i^{Final}\}$
I	Clinical trial phases
K	Processing tasks
$\mathbf{K}_m$	Processing tasks associated with material *m*
$\mathbf{K}_e^C$	Processing tasks of products in commercialization associated with processing unit *e*
$\mathbf{K}_e^U$	Processing tasks of products under development associated with processing unit *e*
L	Lots
$\mathbf{L}_m$	Lots associated with raw material $m \in \mathbf{W}$
M	Materials including raw materials, intermediaries and final products
P	Final products
$\mathbf{P^C}$	Final products in commercialization
$\mathbf{P^U}$	Final products under development
W	Raw materials
$\mathbf{W}_p$	Raw materials of final product *p*

Parameters

v_{km}	Production rate (positive value for production, and negative value for consumption) of each task *k* and material *m*

τ	Length of each period
$\bar{\tau}_{ke}^{var}$	Time required per unit of processed material
τ^{chg}	Changeover time
$\hat{\tau}_e$	Installation and commissioning time of each processing unit *e* added to the plant
β_{ke}^{max} / β_{ke}^{min}	Maximum and minimum capacity for task *k* in processing unit *e*
μ_m^{max}	Maximum availability of material *m*
$\mu_m^{initial}$	Initial availability of material *m*
σ_{ml}	Lot size of lot *l* associated to raw material $m \in \mathbf{W}$
ω_{mt}	Product demand for material *m* at period *t*
θ_i^I /θ_i^F	Initial and final times for clinical trial phase *i*
γ_{mt}	Maximum number of lots for raw material $m \in \mathbf{W}$ at period *t*
δ_e^{init}	Number of processing units *e* initially available
π_m	Sales price for materials $m \in \mathbf{P}$
$\alpha_k^{oper.}$	Operational cost of each processing task *k*
$\alpha_m^{stor.}$	Storage cost for each material *m*
α_m^{waste}	Cost of disposing each unit of material *m*
α_e^{chg}	Changeover costs associated to each processing unit *e*
$\alpha_{ml}^{lot\ size}$	Cost associated with the lot size *l* for raw material $m \in \mathbf{W}$
$\alpha_e^{invest.}$	Investment costs for each new additional processing unit *e*

Continuous variables

B_{klt}	Batch size of task *k* of lot *l* at period *t*, expressed in kg
D_{mlt}	Amount delivered of each material *m* of lot *l* at period *t*, expressed in kg
R_{mlt}	Excess resource for each material *m* of lot *l* at each period *t*, expressed in kg
$W_{ml}\|_{t=t_i^F}$	Excess amount of final product under development ($m \in \mathbf{P^U}$) of lot *l* considered waste at the end of each clinical trial *i* ($t = t_i^F$), expressed in kg
F_e	Capacity unused for each processing unit *e*, expressed in hours

Binary variables

Y_{plet}	=1 if product *p* is assigned to processing unit *e* and lot *l*, at period *t*

Integer variables

N_{klt}	Number of instances of task *k* of lot *l* at period *t*
A_{et}	Number of additional processing units *e* to add to the plant at period *t*
L_{mlt}	Number of lots *l* of raw material $m \in \mathbf{W}$ at period *t*
Z_{pelt}	Process design variable for each product *p* of lot *l* assigned to processing unit *e* at period *t*

5.1.1. Constraints

$$\sigma_{ml} L_{mlt} = -\sum_{k \in \mathbf{K}_m} \nu_{km} B_{klt} \qquad \forall p \in \mathbf{P}, m \in \mathbf{W}_p, l \in \mathbf{L}_m, t \in \mathbf{H} \tag{1}$$

$$\sum_{e \in \mathbf{E}_m} Y_{plet} \leq L_{mlt} \leq \gamma_{mt} \sum_{e \in \mathbf{E}_m} Y_{plet} \qquad \forall p \in \mathbf{P}, m \in \mathbf{W}_p, l \in \mathbf{L}, t \in \mathbf{H} \tag{2}$$

$$Y_{plet} + Y_{pl\prime et\prime} \leq 1 \quad \forall p \in \mathbf{P}, e \in \mathbf{E}_p, l, l' \in \mathbf{L}_m : l' > l, t \in \mathbf{H}, t' = \{0 \dots t\} \tag{3}$$

$$R_{mlt} = \left(\mu_m^{initial}|_{t=0}\,,\ R_{m,t-1}|_{t>0}\right) + (\sigma_{ml} L_{mlt})|_{m \in \mathbf{W}} + \sum_{k \in \mathbf{K}_m} \nu_{km} B_{klt} - D_{mlt}|_{m \in \mathbf{P}} - W_{mlt}|_{m \in \mathbf{P^U}, t=\theta_i^F} \quad \forall m \in \mathbf{M}, l \in \mathbf{L}, i \in \mathbf{I}, t \in \mathbf{H} \tag{4}$$

$$0 \leq \sum_{l \in \mathbf{L}} R_{mlt} \leq \mu_m^{max} \quad \forall m \in \mathbf{M}, t \in \mathbf{H} \tag{5}$$

$$R_{ml}|_{t=\theta_i^F} = 0 \quad \forall m \in \mathbf{P^U}, l \in \mathbf{L}, i \in \mathbf{I}, t \in \mathbf{H} \tag{6}$$

$$\sum_{l \in \mathbf{L}} D_{mlt} = \omega_{mt} \quad \forall m \in \mathbf{P}, t \in \mathbf{H} \tag{7}$$

$$D_{mlt} = 0 \quad \forall m \in \mathbf{M} \backslash \mathbf{P}, l \in \mathbf{L}, t \in \mathbf{H} \tag{8}$$

$$\beta_{ke}^{min} N_{klt} \leq B_{klt} \leq \beta_{ke}^{max} N_{klt} \quad \forall e \in \mathbf{E}, k \in \mathbf{K}_e, l \in \mathbf{L}, t \in \mathbf{H} \tag{9}$$

$$Y_{plet} \leq B_{klt} \leq bigM Y_{plet} \quad \forall p \in \mathbf{P}, e \in \mathbf{E}, k \in \mathbf{K}_e, l \in \mathbf{L}, t \in \mathbf{H} \tag{10}$$

$$\sum_{l \in \mathbf{L}} \sum_{k \in \mathbf{K}_e^C} B_{klt}\, \bar{\tau}_{ke}^{var} + \sum_{l \in \mathbf{L}} \sum_{p \in \mathbf{P}^C} Y_{plet}\, \tau^{chg} - \tau^{chg} + F_e \leq \delta_e^{init}\, \tau \quad \forall e \in \mathbf{E}, t \in \mathbf{H} \tag{11}$$

$$\sum_{l \in \mathbf{L}} \sum_{k \in \mathbf{K}_e^U} B_{klt}\, \bar{\tau}_{ke}^{var} + \sum_{l \in \mathbf{L}} \sum_{p \in \mathbf{P}^U} Y_{plet}\, \tau^{chg} - \tau^{chg} \leq F_e + \sum_{t\prime=0}^{t-1} A_{et\prime}\tau + A_{et}(\tau - \hat{\tau}_e) \quad \forall e \in \mathbf{E}, t \in \mathbf{H} \tag{12}$$

$$Z_{plet} \geq Y_{plet} - Y_{ple,t-1} \quad \forall e \in \mathbf{E}, p \in \mathbf{P}_e, l \in \mathbf{L}, t \in \mathbf{H} \tag{13}$$

$$\sum_{t \in \mathbf{H}} Z_{plet} \leq 1 \quad \forall e \in \mathbf{E}, p \in \mathbf{P}_e, l \in \mathbf{L}, t \in \mathbf{H} \tag{14}$$

$$\begin{aligned} R_{mlt} &\in \mathbb{R}_+ \quad \forall m \in \mathbf{M}, t \in \mathbf{H} \\ B_{klt} &\in \mathbb{R}_+ \quad \forall k \in \mathbf{K}, t \in \mathbf{H} \\ W_{mlt} &\in \mathbb{R}_+ \quad \forall m \in \mathbf{P^U}, t \in \mathbf{H} \\ D_{mlt} &\in \mathbb{R}_+ \quad \forall m \in \mathbf{P}, t \in \mathbf{H} \\ F_e &\in \mathbb{R}_+ \quad \forall p \in \mathbf{P^C}, e \in \mathbf{E} \\ N_{klt} &\in \mathbb{Z}_+ \quad \forall k \in \mathbf{K}, t \in \mathbf{H} \end{aligned} \tag{15}$$

$$L_{mlt} \in \mathbb{Z}_+ \qquad \forall\, m \in \mathbf{W}, l \in \mathbf{L}_w, t \in \mathbf{H}$$

$$Y_{plet} \in \{0,1\} \qquad \forall p \in \mathbf{P}, e \in \mathbf{E}, t \in \mathbf{H}$$

$$A_{et} \in \mathbb{Z}_+ \qquad \forall e \in \mathbf{E}, t \in \mathbf{H}$$

$$Z_{plet} \in \mathbb{Z}_+ \qquad \forall\, p \in \mathbf{P}, e \in \mathbf{E}, t \in \mathbf{H}$$

Constraints (1) to (3) are used to model the lot-size and scale-up decisions based on the starting raw material of each final product *p*. Constraint (1) guarantees that the total amount available of raw material $m \in \mathbf{W}$ of lot *l* at each time period is equal to the total amount consumed by the respective tasks $k \in K_m$ of lot *l*. The parameters σ_{ml} on the left hand side of this constraint represent the lot-sizes of lot *l* for each raw material $m \in \mathbf{W}$, and the ν_{km} parameters on the right hand side take a negative value corresponding to the consumption rate of each task *k* and raw material *m*. Constraints (2) bound the number of lots of each lot-size *l* (L_{mlt}) to a given maximum value (γ_{mt}) for each starting raw material *m* associated with final product *p* ($m \in \mathbf{W}_p$) and period *t*. These constraints also guarantee that the number of lots will be zero if no product *p* of lot *l* is assigned to processing unit *e*, at period *t* (i.e. $Y_{plet} = 0$). Finally, constraints (3) model the scale-up decisions, by ensuring that the size of the lots never decreases during the planning horizon.

The excess resource balances are defined by constraints (4) in which the continuous variables R_{mlt} denote the material availability over time, for each material *m* of lot *l*. The parameters $\mu_m^{initial}$ represent the initial material availability for each material *m* (being 0 for final products and intermediaries). The second term of constraints (4) is activated only for raw materials, and it defines the starting raw material quantity, that is limited by the given lot-sizes (σ_{ml}). The total amount produced or consumed by each task is defined by the third term of these constraints in which the parameters ν_{km} denote the proportion of material that is consumed (negative values) or produced (positive values) during the execution of the task.

This modelling approach has been introduced by Pantelides (1994). The continuous variables D_{mlt} define the amount of material delivered in each period, being 0 for all materials except final products ($m \in \mathbf{P}$). The last term will be activated only for products under development, and it corresponds to the leftovers of the final product, at the end of each clinical trial phase *i* (to be considered as wastage).

Constraints (5) define the excess resource capacity for each material and time interval, bounded by the given maximum materials availability μ_m^{max}. Furthermore, since the excess amount of final products under development at the end of each clinical trial phase must be discarded and cannot be used in the following periods, expression (6) is introduced to ensure that the material availability of these products is 0 at the end of each clinical trial phase.

Constraints (7) define the production requirements to meet the given demand (ω_{mt}), and expression (8) guarantees that only final products can be delivered.

Constraints (9) ensure that the total amount of material processed (B_{klt}) is bounded by the minimum and maximum processing unit capacities (β_{ke}^{min}/ β_{ke}^{max}). The integer variable N_{klt} is defined as the number of instances (batches) of task *k*, for lot *l*, in period *t*.

Constraints (10) are very similar to constraints (2) defined earlier, but even though they are necessary, since constraints (2) apply only for the starting raw materials *m* ($m \in \mathbf{W}$). These additional constraints (10) are then used to activate the decision variables B_{klt} (total amount processed) associated to all tasks *k* ($k \in \mathbf{K}_e$), and to force those variables to be 0 if no product *p* of lot *l* is assigned to processing unit *e* at period *t* (i.e. $Y_{plet} = 0$). The $bigM$ represents a very large number (in relative terms), and Y_{plet} are the binary variables for process activation.

Constraints (11) and (12) define the production capacity, expressed in the total time availability for processing unit *e* and period *t*. Given that only capacity extensions for products under development are allowable in this formulation, a distinction must be done regarding the two types of products. Thus, constraints (11) denote the production capacity for products in commercialization, and constraints (12) for products under development. The first summation in (11) represents the total time required for the execution of tasks *k*, in which the coefficient $\bar{\tau}_{ke}^{var}$ is known and denotes the time required per unit of processed material. The second summation defines the changeover times associated to equipment and lot changing. Parameter τ^{chg} represents the changeover time. A third term (τ^{chg}) is added to constraints (11) in order to ensure that the number of changeovers is equal to the number of products minus one. This is needed to

prevent an overestimation of the changeover times across adjacent periods in which the last product of the previous period is equal to the first product of the following period (Grossmann, 2007). The last term (F_e) expresses the capacity of each processing unit *e* unused by the products in commercialization. This free capacity will be used as available capacity for the products under development in constraints (12). The right hand side of these constraints is the total available capacity of each processing unit *e*, in each period. The parameters δ_e^{init} and τ are given, and denote respectively the number of processing units *e* initially available at the plant and the length of each period *t*. In constraints (12), the left hand side is equal to constraints (11), except for the decision variables F_e, that, in this case, are in the right hand side, as they reflect the available capacity for the production of the under development products. However, because this available capacity is very limited, it is likely that some adjustments to the process design will be needed, and some capacity extensions performed. Accordingly, integer variables A_{et} are introduced in constraints (12), to determine the additional amount of capacity (expressed in additional time) required for the production of each product p ($p \in \mathbf{P^U}$) in processing unit *e*. Thus, the second term in the right hand side of these constraints refers to the total capacity added in previous periods (t = 0,…,t-1). This term guarantees that, if an increase in capacity occurs, the new processing units added to the plant will be available during the following periods until the end of the planning horizon. Finally, the last term of these constraints denote the capacity extensions to be performed in period *t*, also reflecting the time required for the installation and commissioning of the added units before they are ready to start operating ($\hat{\tau}_e$).

Constraints (13) and (14) are process design constraints needed to ensure that, after a processing unit has been selected for a given process, it cannot leave that process in a given period and be later assigned again to the same process (i.e., in a period ahead). Finally, expressions (15) are used to define the domain of the variables.

Objective Function

As referred above, and in order to reflect in the model the main concerns of the company, we have considered as objective function (eq. (16)) the maximization of the Net Present Value (NPV) of the operations related to these projects. This measure depends on the income from sales over the planning horizon (INCO) minus the operational costs (*OC*), storage costs (*SC*), disposal costs for wasted final products (WC), changeover costs (*COC*), scale-up costs (LC), and investment costs (*IC*) (costs associated with capacity extension):

$$\max NPV = INCO - OC - SC - WC - COC - LC - IC \tag{16}$$

Considering the discount factor (d_t) given by expression (17), where r is the interest rate and *t* the period (Bagajewicz, 2008), each term of the objective function (16) can be described individually as presented below.

$$d_t = \frac{1}{(1+r)^t} \quad \forall\, t \in \mathbf{H} \tag{17}$$

The income over the planning horizon results from the final product sales, and is given by expression (16)a, where π_m denotes the given sale prices for each material *m*.

$$INCO = \sum_{t\in\mathbf{H}} d_t \sum_{l\in\mathbf{L}} \sum_{m\in\mathbf{P}} \sum_{t\in\mathbf{H}} (\pi_m D_{mlt}) \tag{16a}$$

The operational costs are associated with each task *k*, and are given by expression (16)b, where $\alpha_k^{oper.}$ is the operational cost of task *k*.

$$OC = \sum_{t\in\mathbf{H}} d_t \sum_{l\in\mathbf{L}} \sum_{k\in\mathbf{K}_e} \sum_{t\in\mathbf{H}} \left(\alpha_k^{oper.} N_{klt}\right) \tag{16b}$$

Storage costs are also considered in this model, and they are given by eq. (16)c, where $\alpha_m^{stor.}$ represents the holding costs for each material *m*.

$$SC = \sum_{t\in\mathbf{H}} d_t \sum_{l\in\mathbf{L}} \sum_{m\in\mathbf{M}} \sum_{t\in\mathbf{H}} (\alpha_m^{stor.} R_{mlt}) \quad (16)c$$

The costs associated to the disposal of unused final products under development (waste) are given by expression (16)d.

$$WC = \sum_{t\in\mathbf{H}} d_t \sum_{l\in\mathbf{L}} \sum_{m\in\mathbf{P^U}} \sum_{t\in\mathbf{H}} (\alpha_m^{waste} W_{mlt}) \quad (16)d$$

The changeover costs are given by eq. (16)e, where the given parameters α_e^{chg} denote the changeover costs associated to each processing unit *e*.

$$COC = \sum_{t\in\mathbf{H}} d_t \sum_{l\in\mathbf{L}} \sum_{e\in\mathbf{E}} \sum_{p\in\mathbf{P}} \sum_{t\in\mathbf{H}} \left(\alpha_e^{chg} Y_{plet}\right) \quad (16)e$$

The costs associated to the scale-ups are given by eq. (16)f, where $\alpha_{ml}^{lot\ size}$ denotes the cost associated to the selection of the lot size *l* for the starting raw material *m*.

$$LC = \sum_{t\in\mathbf{H}} d_t \sum_{m\in\mathbf{W}} \sum_{l\in\mathbf{L}_w} \sum_{t\in\mathbf{H}} \left(\alpha_{ml}^{lot\ size} L_{mlt}\right) \quad (16)f$$

Finally, if a capacity expansion occurs ($A_{et} > 0$), an investment cost must be considered for each new processing unit that is added to the plant. These costs are given by eq. (16)g, where the parameters $\alpha_e^{invest.}$ are the investment costs associated to each new processing unit *e* added to the plant.

$$IC = \sum_{t\in\mathbf{H}} d_t \sum_{e\in\mathbf{E}} \sum_{t\in\mathbf{H}} (\alpha_e^{invest.} A_{et}) \quad (16)g$$

6. Mathematical Results and Discussion

6.1. Case description

To validate the proposed framework and demonstrate its applicability, a case was designed based on a real problem of the chemical-pharmaceutical industry. In this case, the product portfolio is composed by 3 new products (PA, PB, and PC) entering the product development phase, and by 2 products (PD and PE) already in commercialization. A planning horizon of 5 years is considered, discretized into 10 periods of 6 months each (4032 hours for a plant, operating 24 hours a day and 7 days a week). The demand forecast profiles for the entire planning horizon and for each product are presented in Figure 4. To accommodate the three phases for the clinical trials, the planning horizon is divided, with 1.5 years to conduct each of the clinical trials phases I and II, and with 2 years for clinical trial phase III (see Figure 4).

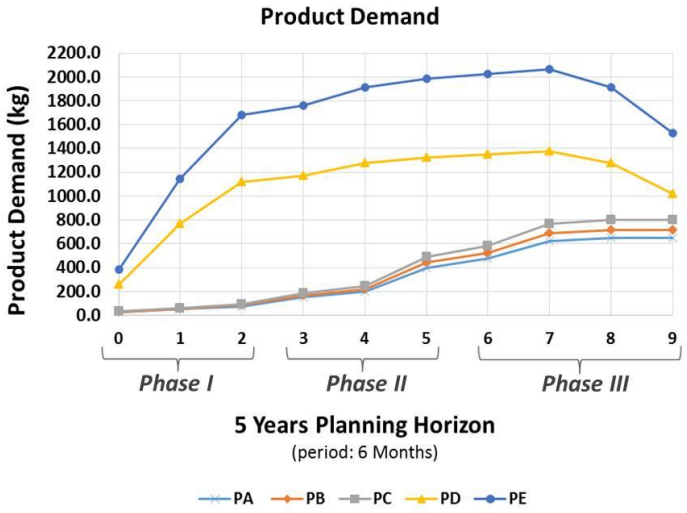


Figure 4. Demand profile for products under development (PA, PB and PC) and products already in commercialization (PD and PE) (Sundaramoorthy et al., 2012)

All products follow a similar production recipe in which the task sequence, unit suitability, reaction yields, and processing times are clearly identified (see Figure 5). All processes are composed by 3 aggregate tasks that can be processed in 3 possible unit types ({R1, R2, R3}, {F1, F2, F3}, and {D1, D2, D3}) with different capacities, and different operational and investment costs (see Figure 6). These tasks have a variable duration (expressed in hour/kg) that is proportional to the batch size. Moreover, each product can only be produced in pre-determined lot-sizes, with four different lot-sizes defined for each product.

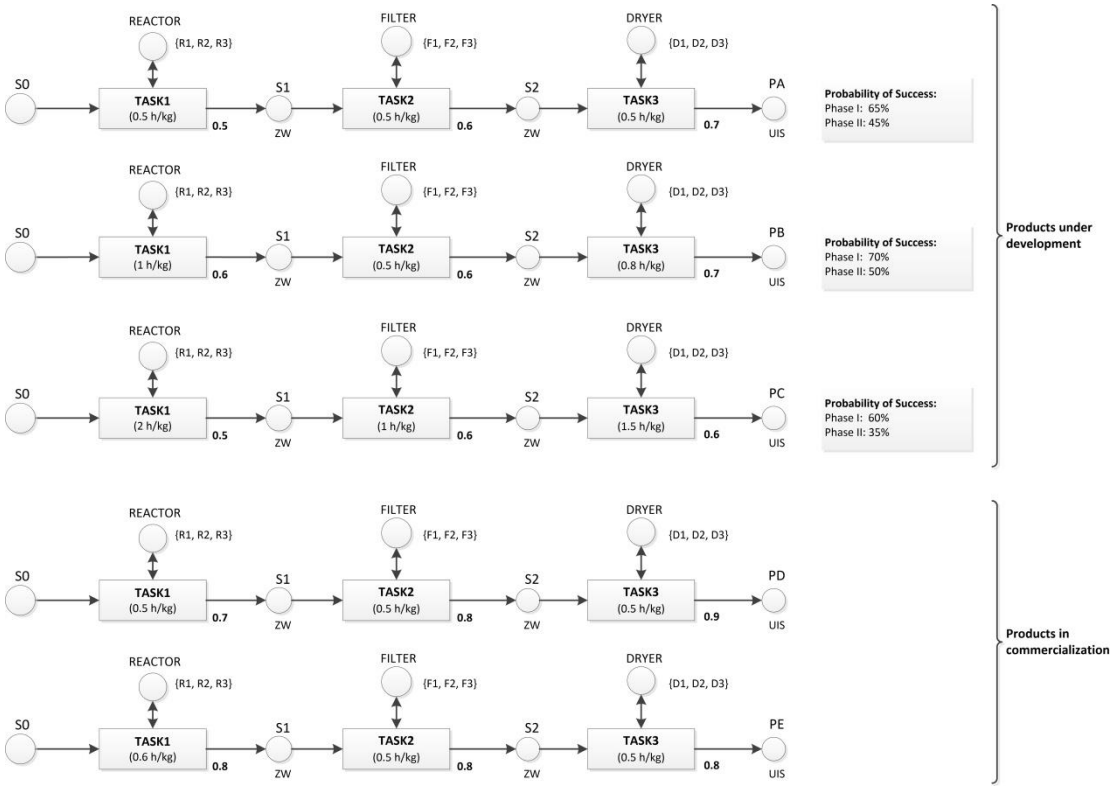


Figure 5. Product recipes and probabilities of success for the products under development and for the products already in commercialization.

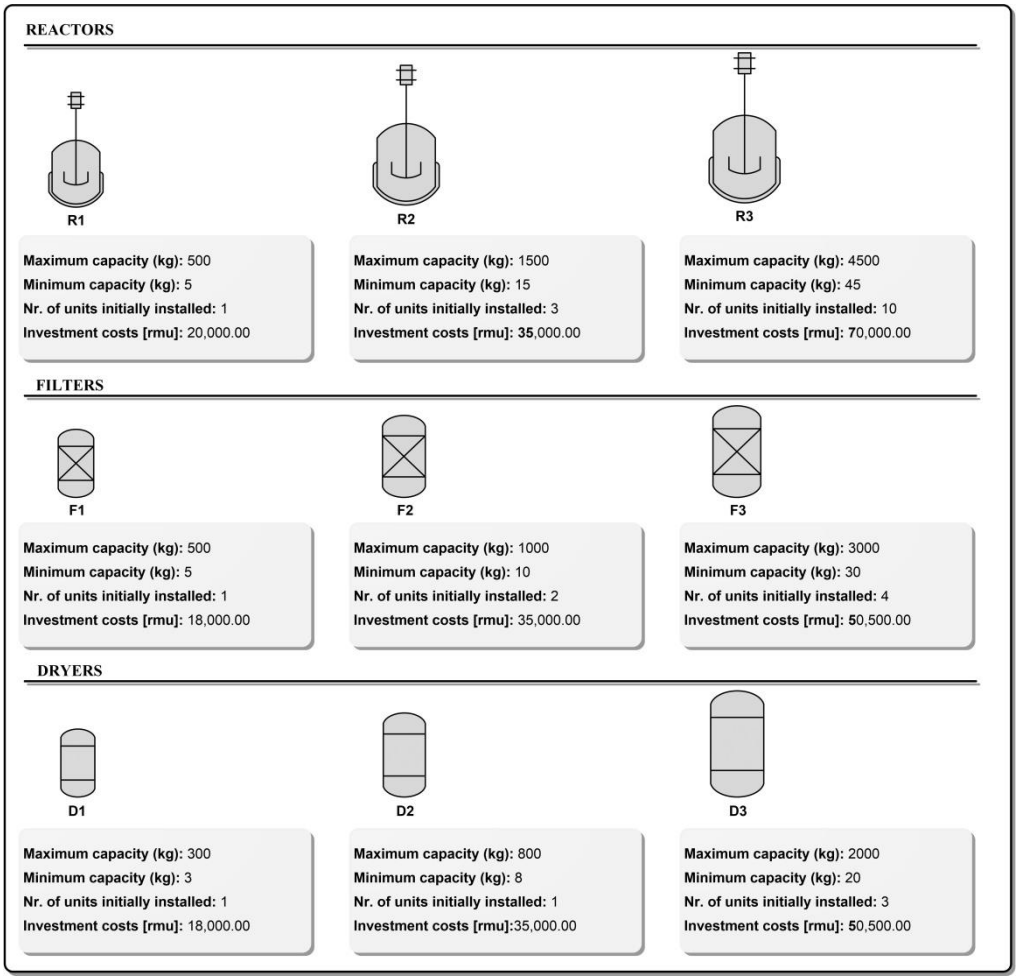


Figure 6. Processing unit types and their maximum and minimum capacities.

To reflect the uncertainty of product demand, normal distributions are used with values, per period, for the mean and standard deviations, derived from the profiles presented in Figure 4. We have considered a standard deviation of 30% for the products under development, and 10% for the products in commercialization, since less demand variability is expected in this case. On the other hand, to capture the uncertainty associated to the clinical trials (pass/fail outcomes), Bernoulli distributions are used, considering the success probabilities depicted in Figure 5, and based on the available information from the literature (Fisher et al., 2015).

6.2. Computational results

The MILP model was implemented using IBM ILOG CPLEX Optimization studio, version 12.5.1, running on an Intel Xeon at 3.33 GHz machine with 24 GB of RAM. As stopping criterion, we considered a time limit of 3600 seconds, and an *integrality gap* of 5%. For the simulation component (MCS), an iterative model was also implemented in ILOG/CPLEX, and 1000 iterations were performed by randomly generating the uncertainty parameters from given probability distributions (normal and Bernoulli distributions). For each iteration, a solution was found and the frequency of occurrence for each decision variable was determined and analysed. The MCS for the 1000 iterations took a total of 36 hours to be completed, with an average run time, for each iteration, of 129.35 seconds. The *integrality gap* ranges from a minimum of 1.43% to a maximum of 5.0% (according to the stopping criterion referred above). The main computational statistics are described in Table 1.

Table 1. Computational statistics

binary variables	integer variables	continuous variables	constraints	B&B nodes*	optimality gap (%)*	CPU time (seconds)*
1,800	3,890	3,554	29,160	10,356.29	3.8	129.35

* Average values for the 1000 iterations.

6.2.1. NPV analysis

The results obtained are presented in Figure 7, with the NPV histogram and the associated probability distribution. The resulting histogram presents a slightly skewed right pattern, due to the fact that the NPV highest values occur in the instances in which all products under development successfully pass all clinical trial phases, this fact having a very low frequency of occurrence, as it is highly unlikely to happen.

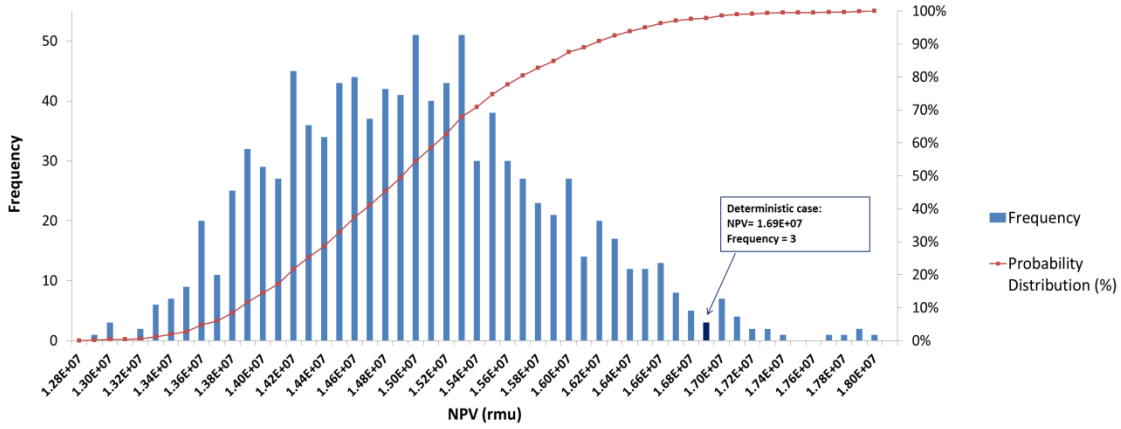


Figure 7. NPV histogram and associated probability distribution.

The maximum NPV value obtained was 1.79 x 10^7 relative monetary units *(rmu);* the minimum value was 1.28 x 10^7 *rmu* and the average NPV was 1.50 x 10^7 *rmu*. The variation between the average and the minimum values is about 14%, which may be more or less penalizing for the company, depending on the particular context, the main established goals, and the risk aversion of the decision makers.
On the other hand, the optimal profit for the deterministic reference case, which is based on the forecast values illustrated in Figure 4 was 1.69 x 10^7 *rmu*. According to Figure 7, the frequency of occurrence of this value is just 3 in 1000 iterations, and the probability of the profit to be below this value is about 98% (see Figure 7), this meaning that the deterministic case is very unlikely to occur. These results clearly show that the decision-making process for a 5 years capacity planning entails a considerable risk if we only consider a deterministic analysis.

6.2.2. Scale-up analysis

The determination of the lot-sizes to be produced and of the scale-ups to be performed are very important decisions in the chemical-pharmaceutical industry. From a strict cost point of view, the production of larger, fewer lots is more desirable, as demonstrated in (Samuel Moniz, Barbosa-Povoa, et al., 2014). Here, the results show that the most frequently selected lot-sizes and scale-ups over the entire planning horizon are in accordance with the previous statement, since there is a clear preference for single lots, particularly for the under development products. Exceptions occur when the demand is very high. Since no backlogs are allowed, when demand is high the model is forced to select several lots of a certain size in order to completely meet the product demand.

The histograms in Figure 9 and in Figure 10 are for the products under development, and for the products in commercialization, respectively. These histograms only present the lot-sizes that are more frequently selected by the model in each period. For example, for product PA, at period t=0, all the lot-sizes selected by the model are depicted in Figure 8. However, only the most frequently selected (1L3_200) lot-size was picked for the histogram in Figure 9a). This procedure was performed for all products and periods.

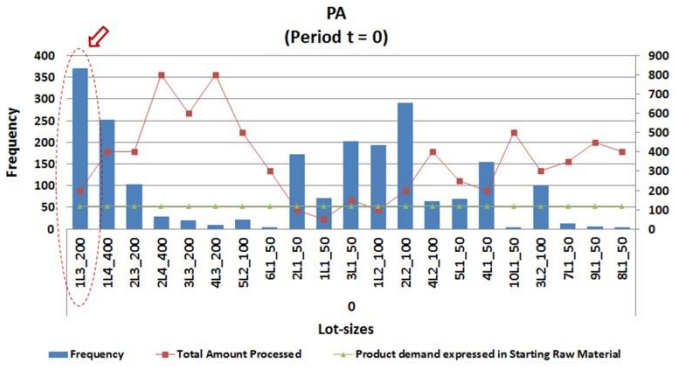
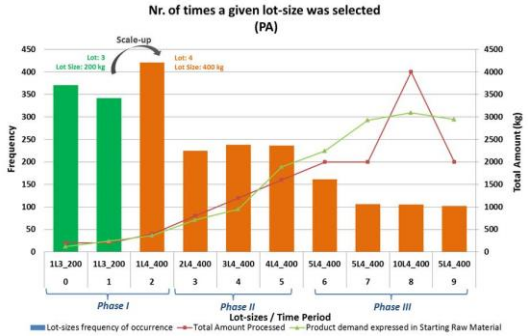


Figure 8. Selected lot-sizes for product PA, at period t=0.

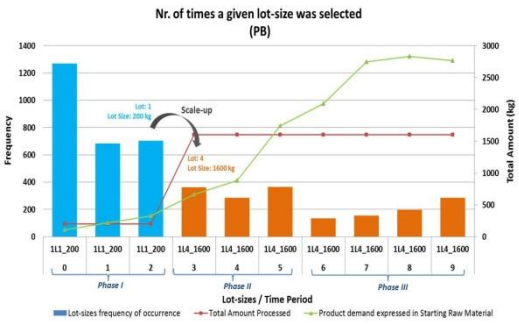
When analysing the histograms of both types of products, we can notice that in the first case (products under development), there is a considerable decrease in the frequency values in each clinical trial phase, this being a direct consequence of the pass/fail probabilities associated to the products. For the products in commercialization, this decrease does not occur due to their much more stable demand.

According to Figure 9, the most frequently selected lot-sizes for the products under development are: lot 3 and lot 4, for product PA; lot 1 and lot 4, for product PB; and finally, lot 1, lot 2, lot 3 and lot 4, for product PC. These values correspond to one scale-up for product PA and product PB, and three scale-ups for product PC, over the planning horizon. In all the three products, we can observe that the scale-ups are closely related to the clinical trial phases, even if this is more evident in the case of product PC, because of the higher values of the product demand. In that sense, for product PA, it seems reasonable to consider lot 3 for clinical trial phase I, and lot 4 for the other two clinical trial phases. For product PB, it is clear that the most suitable lot for phase I is lot 1, and lot 4 for the last two clinical trials phases. Finally, for product PC, it seems reasonable to consider lot 1 for clinical trial phase I, lot 2 and 3 for clinical trial phase II, and lot 4 for clinical trial phase III. On the other hand, for products in commercialization (PD, and PE), the larger lot (lot 4) is the most frequently selected, due to the larger and more stable values for the product demand. This is particularly evident for product PE that presents a higher product demand for almost the entire planning horizon.

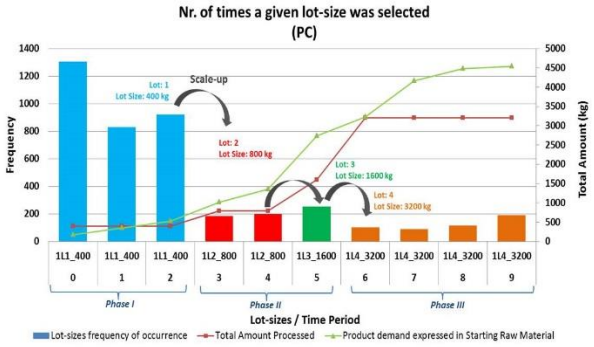
It is worth to notice that the product demand and the total amount processed (depicted in Figure 9 and in Figure 10) correspond to the starting raw materials associated to each final product, and derived from the forecasted values presented in Figure 4 (considering the associated production yields).



(a)

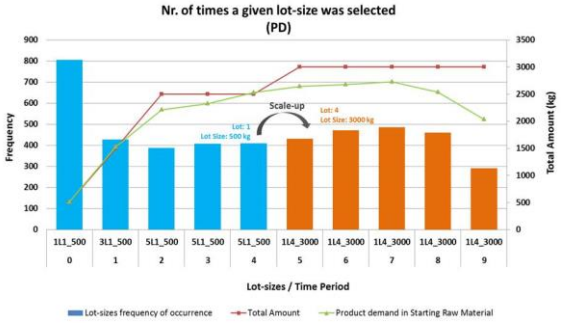


(b)

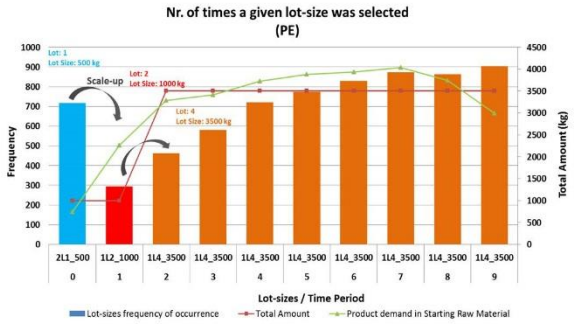


(c)

Figure 9. Lot-size and scale-up decisions for products under development: (a) product PA, (b) product PB, and (c) product PC.



(a)



(b)

Figure 10. Lot-size and scale-up decisions for products already in commercialization: (a) product PD, and (b) product PE.

Finally, the most likely process design configurations for each product and clinical trial / planning period were determined. In the next section, the trade-offs between process design configuration and scale-ups are analysed.

6.2.3. Process design and scale-up analysis

These results also allow us to identify the sets of processing units associated with the lot-sizes that have been selected with higher probabilities. They are presented as histograms in Figure 11 (a1, b1, c1), and in Figure 12 (d1, e1), for the products under development and in commercialization, respectively. In this case, the histograms were obtained by considering the three or four most frequently selected process configurations.

We can also see that, when simultaneously considering process design and lot-size configuration, the most selected process designs seem to lead to more scale-ups (2 or 3) than in the previous analysis (with just scale-ups). This seems to show that the model tends to favor the process design stability over scale-ups and lot size increases. This is an interesting result, satisfying some of the main goals of the problem, such as the enhancement of process stability, the minimization of process changes, and the preservation of its life cycle.

However, based on these results, it is not possible to guarantee that the most selected process configurations in each period / clinical trial phase, are obtained in the same iteration of the simulation framework. Thus, in order to minimize possible misinterpretations of the results, a robustness measure for each process design configuration was developed. This measure is computed for the three or four process designs more frequently selected in each period, and reflects the percentage in which each process is repeated in more than two periods in the same iteration. These results are illustrated in Figure 11 (a2, b2, c2) for products under development, and in Figure 12 (d2, e2) for products in commercialization.

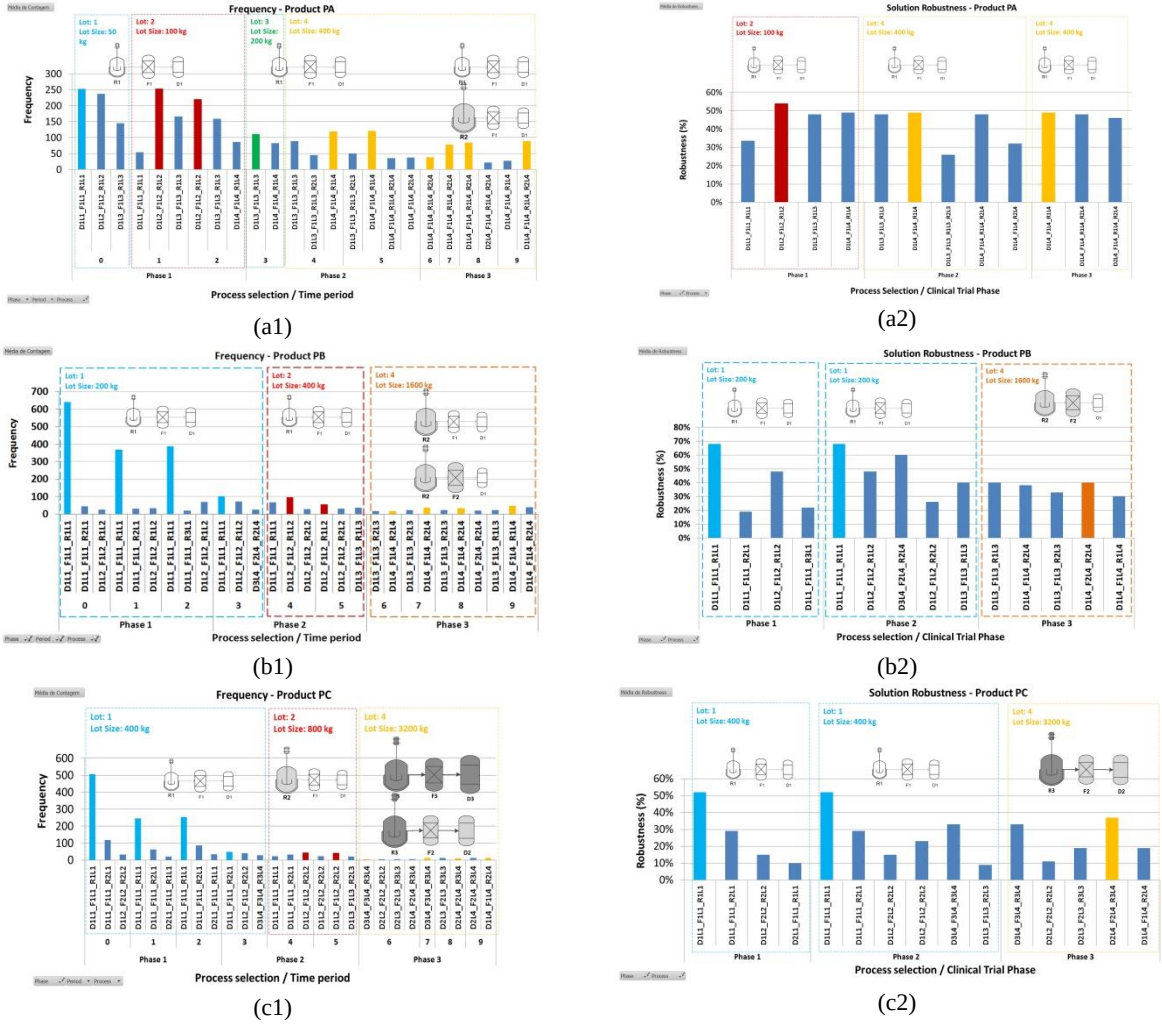


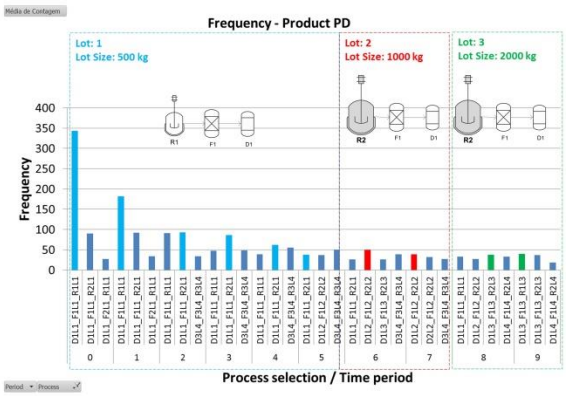
Figure 11. Process design selection and solution robustness for the products under development.

A combined analysis of the two results (frequency histograms and robustness charts) can be used to support the decision-making process in a more reliable way. Thus, from this analysis, it seems plausible to consider that the process design configuration {R1, F1, D1} is the most suitable for product PA, with one scale-up at the end of the clinical trials phase I, from lot 2 (100 kg) to lot 4 (400 kg). Similarly, for product PB, the process design configuration {R1, F1, D1} seems to be the most adequate decision for clinical trials phases I and II, and {R2, F2, D1} for the last clinical trial phase. Also in this case, one scale-up occurs, but at the end of clinical trials phase II, from lot 1 (200 kg) to lot 4 (1600 kg). Finally, for product PC, it seems reasonable to consider that the most suitable process design configuration is {R1, F1, D1} for clinical trials phases I and II, and {R3, F2, D2} for clinical trials phase III. Again, one scale-up is expected at the end of clinical trials phase II, from lot 1 (400 kg) to lot 4 (3200 kg).

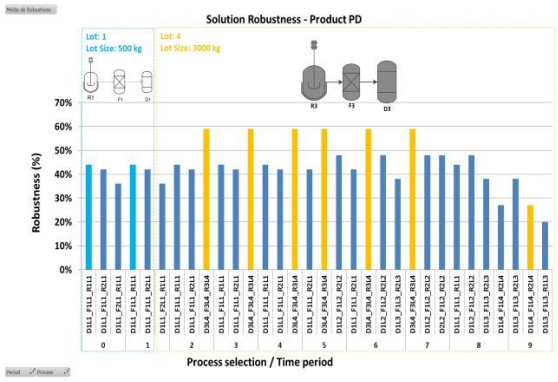
A similar analysis is made for both products in commercialization (PD and PE). For product PD, the best process design configuration seems to be {R1, F1, D1}, associated with lot-size 1 (500 kg) for the first two periods (corresponding to the first year), and {R3, F3, D3}, associated with lot-size 4 (3000 kg) for the rest of the planning horizon. For product PE, the most frequently selected and robust process design configuration is {R2, F1, D1} for the entire planning horizon, with one scale-up at the end of time period 3 (corresponding to the first 2 years), from lot 2 (1000 kg) to lot 4 (3500 kg).

Additionally, from the analysis of the robustness charts, we can see that in most of the cases, a change in the lot size is accompanied by a change in the process design configuration for higher capacity processing units. This means that lower capacity units tend to be chosen in the lower product demand periods / early stages of development, and the higher capacity units are more frequently selected in the higher product demand periods / last stages of development. Moreover, the higher capacity processing units seem to be

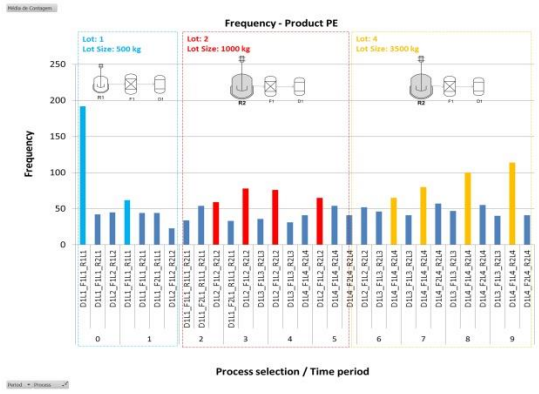
more frequently chosen for the products already in commercialization. In that sense, the model seems to achieve a good trade-off between the capacity of processing units, and both product demand and process stability. Moreover, it is clear from the results obtained for the under development products, that process design configurations and scale-ups are strongly connected to the success of the clinical trials, this showing the relevance of this analysis, that provides reliable information to boost sooner decisions with minimal risk.



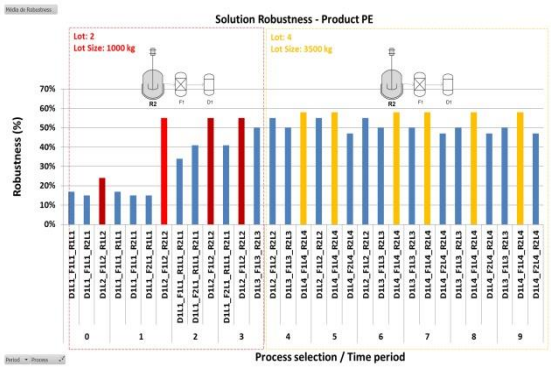
(d1)



(d2)



(e1)



(e2)

Figure 12. Process design selection and solution robustness for the products in commercialization.

When comparing these results to the deterministic case, for the products under development (see table 2), we can see that in the earlier stages of development, the process design configurations are very similar (with the exception of product PB). This can be explained by the fact that one of the initial assumptions in this work was that all the three products enter clinical trial phase I at the same time, and also by the low levels of product demand and high capacity availability at this phase. However, moving forward through the time horizon, to the clinical trial phases II and III, the differences become significant in terms of capacity utilization. It is clear that, in the deterministic case, the decisions tend to benefit higher investments in capacity utilization. For example, in phase III, in almost all cases, the model selects two or more processing units of the same type in the same period. This reveals the conservative nature of the model that, in order not to fail any delivery, tends to oversize both the capacity utilization and the resource allocation. Additionally, according to the previous NPV analysis, the “deterministic case” is very unlikely to occur, this meaning that this high investment in capacity utilization is most likely not to be needed.

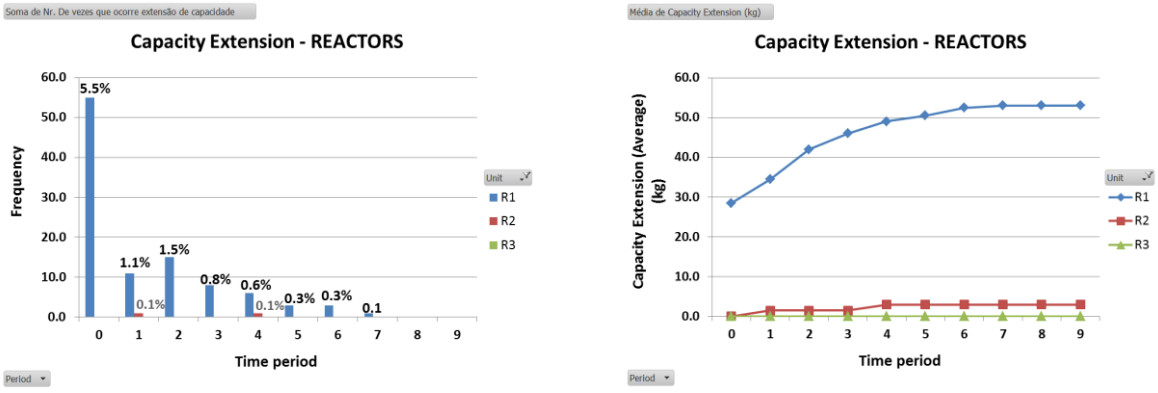
Table 2. Deterministic process design results for the under development products

	Product PA		Product PB		Product PC	
	t	Process	t	Process	t	Process
Phase I	0	D1L2_F1L2_R1L2	0	D1L4_F2L4_R1L4_R2L4	0	D1L1_F1L1_R1L1
	1	D1L2_F1L2_R1L2	1	D1L4_F3L4_R1L4	1	D1L1_F1L1_R1L1
	2	D1L2_F1L2_R1L2	2	-	2	D1L1_F1L1_R1L1
Phase II	3	D1L4_F1L4_R1L4	3	D2L4_F2L4_R1L4	3	D1L1_F1L1_R1L1_R2L1
	4	D1L4_F1L4_R1L4	4	D2L4_F2L4_R1L4	4	D2L1_F1L1_R1L1_R2L1
	5	D1L4_F1L4_R1L4_R2L4	5	D2L4_F1L4_F2L4_R1L4	5	D2L1_F2L1_R1L1_R2L1
Phase III	6	D1L4_F1L4_R1L4_R2L4_R3L4	6	D1L4_F1L4_F2L4_R1L4_R2L4	6	D2L1_F2L1_R1L1_R2L1
	7	D1L4_F1L4_R1L4_R2L4_R3L4	7	D1L4_F1L4_F2L4_R1L4_R2L4	7	D2L2_F2L2_R1L2_R3L2
	8	D1L4_F1L4_R1L4_R2L4_R3L4	8	D1L4_F1L4_F2L4_R1L4	8	D2L2_F2L2_R1L2_R2L2
	9	D1L4_F1L4_R1L4_R2L4	9	D1L4_F1L4_R1L4	9	D2L2_F2L2_R2L2

In this context, the approach proposed in this work can provide valuable and robust information to support the medium and long-term decision-making process, in what concerns production planning and process design configurations, for new drug development. Even if this approach does not give a unique specific solution to the addressed planning problem, it provides robust guidelines for effective decision making, based on several possible solutions, and considering a highly stochastic environment. It also supports the evaluation of the available solutions, considering the process design configurations and their maintenance throughout the entire life-cycle of the possible new commercial drugs.

6.2.4. Capacity extensions and inventory analysis

In the case under analysis, the initial capacity appears to fit the production requirements, since capacity extensions over the entire planning horizon are negligible. In fact, the most significant capacity extensions occur for the *reactors*, particularly for unit R1. Figure 13 shows the histogram (a) and the average capacity extensions in kilograms (b) for the equipment type "reactor". The most substantial capacity extension occurs in the first period, with a probability of occurrence of just 5.5% in the 1000 iterations, this representing an average capacity increase, in the same period, of just 28.5 kg.



(a) (b)

Figure 13. Capacity extension for reactors: (a) frequency of occurrence of a capacity extension, and (b) capacity extension expressed in average of additional capacity in kg, over the 1000 iterations.

On the other hand, when analysing the inventory levels shown in Figure 14, we can see these values are not significant (except for the initial periods when more capacity is available), when compared to the average product demand values presented in Figure 4. The model not only minimizes the amount stored, but also maintains it relatively stable over the entire planning horizon, for all the products (despite the increase in product demand over time). Note that for the products under development (PA, PB, and PC), the inventory drops to 0.0 kg at periods t=2, t=5, and t=9. This is due to the fact that the leftovers at the end of each

clinical trial cannot be reused and therefore they are treated as waste and considered discarded. The average of the wastage levels, for each product under development, is shown in Figure 15.

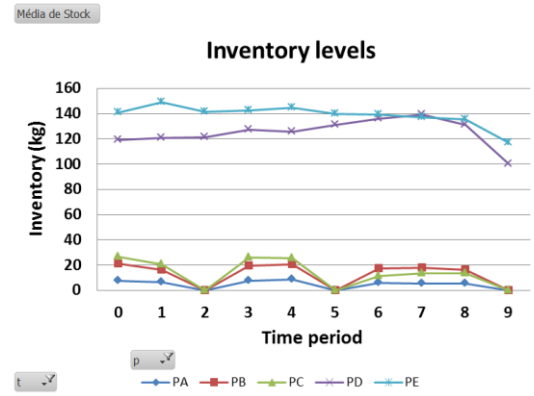


Figure 14. Average levels of inventory over the entire planning horizon, for each product.

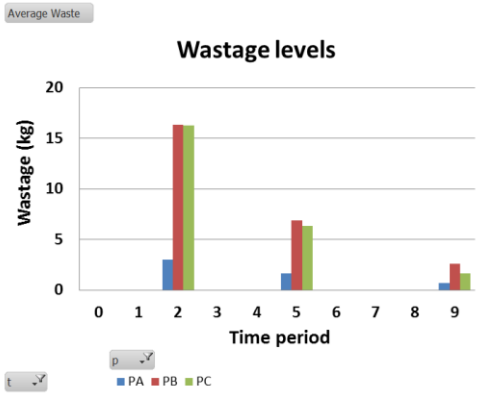


Figure 15. Wastage levels for the products under development, at the end of each clinical trial phase.

These results show that the model is handling well the trade-off between capacity investments and inventory requirements. Moreover, since the model minimizes both types of costs, in order to keep a relatively stable inventory level over the planning horizon, the additional capacity needs are fulfilled by the smallest and cheapest equipment (R1). In this way additional flexibility is added to the plant. Finally, the average values of wastage shown in Figure 15 are really not significant, in particular for periods 5 and 9, with values around 1% and less than 0.5% of the average amount delivered respectively, revealing an efficient resource utilization (this aspect deserving to be further explored in future work). Furthermore, according to Figure 15, the values of wastage are decreasing over the planning horizon, even if the amounts delivered are increasing (contrary to the inventory levels that remain relatively stable), this denoting a good wastage management by the model.

7. Conclusion

This work presents an innovative approach, combining a MILP model and a two-step MCS framework, to address the product-launch planning problem, considering uncertainty on the demand and on the pass/fail clinical trial tests. The MCS component explores the effects of both types of uncertainty, based on normal and Bernoulli distributions, embedded in a two-step sampling procedure. The product-launch planning problem is tackled by integrating both process design and planning decisions, and considering the resource limitations due to resource sharing among products under development and products already in commercialization. A case study inspired on a real situation from the chemical-pharmaceutical industry was used to demonstrate the applicability of the proposed approach. This approach has proven to be able to efficiently assess the effects of uncertainty in process design and scale-up decisions, as well as in capacity and production planning decisions, during new product development.

The obtained results clearly show the significant influence of the uncertainty parameters on the NPV, on the process design configurations, and on the scale-ups, thus strengthening the idea that deterministic models undoubtedly lead to poor decision-making. Particularly in new drug development, the decisions on process design and on scale-ups are strongly dependent on the uncertainty of pass/fail outcomes of the clinical trials. Since these decisions need to be taken before knowing if the new drugs will succeed in all the clinical trial phases, they are extremely critical in economic terms.

The computational results also show that the proposed method is a robust tool to support this decision-making process, by clearly identifying process configurations and scale-ups that maximize profit, in a highly uncertain context. Moreover, the analysis performed in this study can be useful in the long-term assessment of the process design configurations and their lifetime management. It also provides valuable strategic information for developing solutions that not only maximize the NPV, but also reduce the likelihood of the company to undertake process design changes in the future.

We believe that one of the main benefits of this model is the provision of valuable and robust information in early stages of product development, thus supporting an on-time and better decision-making process. Late decisions will therefore be avoided particularly regarding unnecessary or undersized investments, or possible future changes in the process design configuration. Additionally, this comprehensive analysis of the uncertainty parameters will allow a better coordination between the different decision levels within the company, with a clear gain in what concerns decision flexibility.

Nevertheless, one main limitation of this approach (that is, at the same time, an interesting research challenge) is the inability to establish correlations between different process designs, and consequently to determine the unique *here-and-now* solution. As a follow-up of this work, new methodologies are already being developed in order to explore these correlations and to enhance the proposed decision-making framework. Moreover, the application of the framework in more complex instances will clearly allow us to improve the model, and provide a better understanding and exploitation of the proposed methodology. Furthermore, a better systematization of the decision-making process, by including other relevant uncertainty parameters, such as production yields and processing times, should also be addressed. The presented MCS framework proves to be very flexible, allowing the inclusion of additional steps to the sample procedure to account for other uncertainty parameters. Some work has already been done by the authors regarding this matter, particularly with the inclusion of uncertainty in processing times. However, additional uncertainty parameters inevitably increase the computational time, and several alternative solution approaches should be explored in order to minimize this weakness. Finally, further extensions of the model should be considered, to fully explore relevant sustainability aspects, such as waste management and efficient resource utilization, as these issues are rather critical in the pharmaceutical industry.

ACKNOWLEDGEMENT

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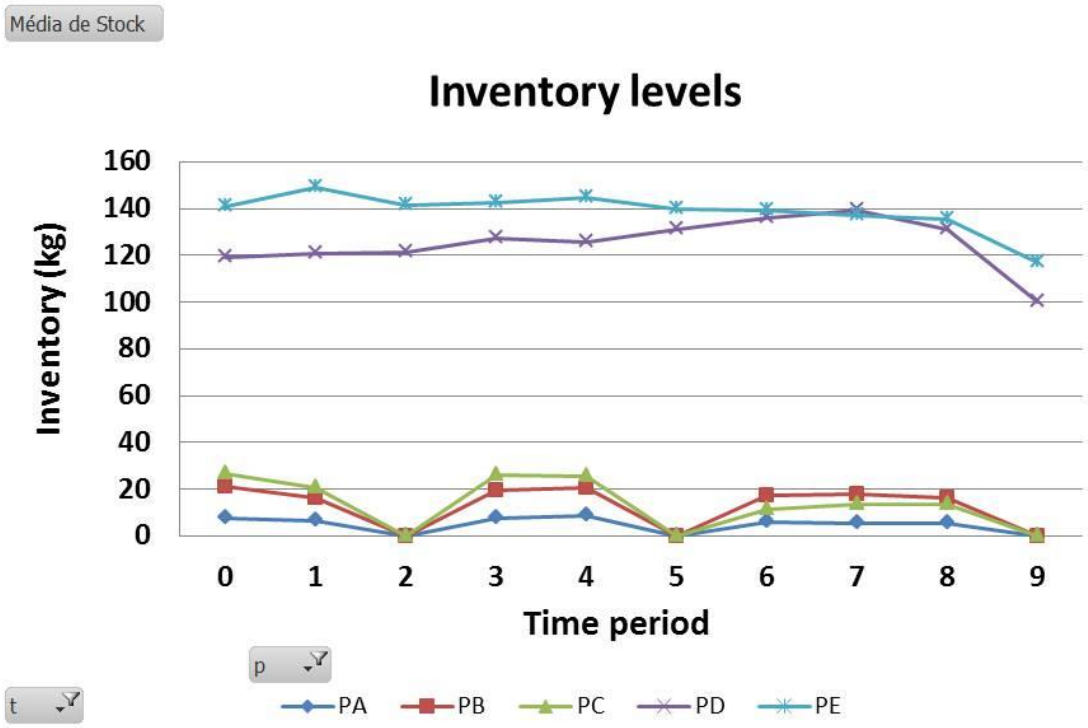
Figure Caption

Figr-1



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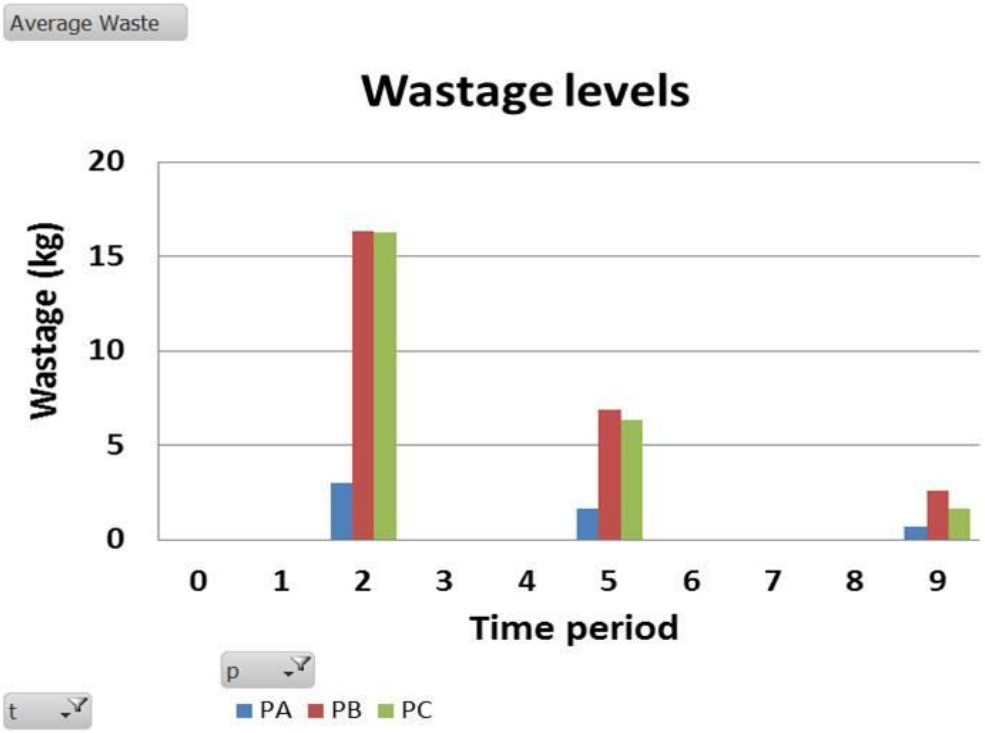

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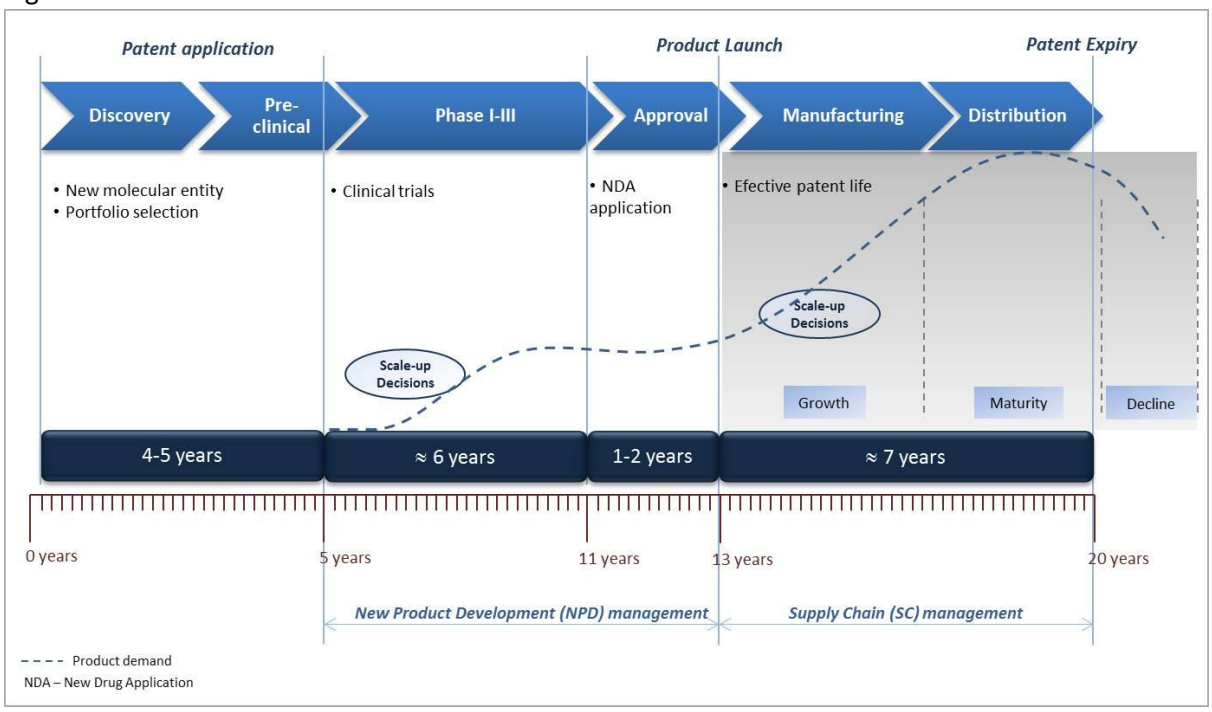

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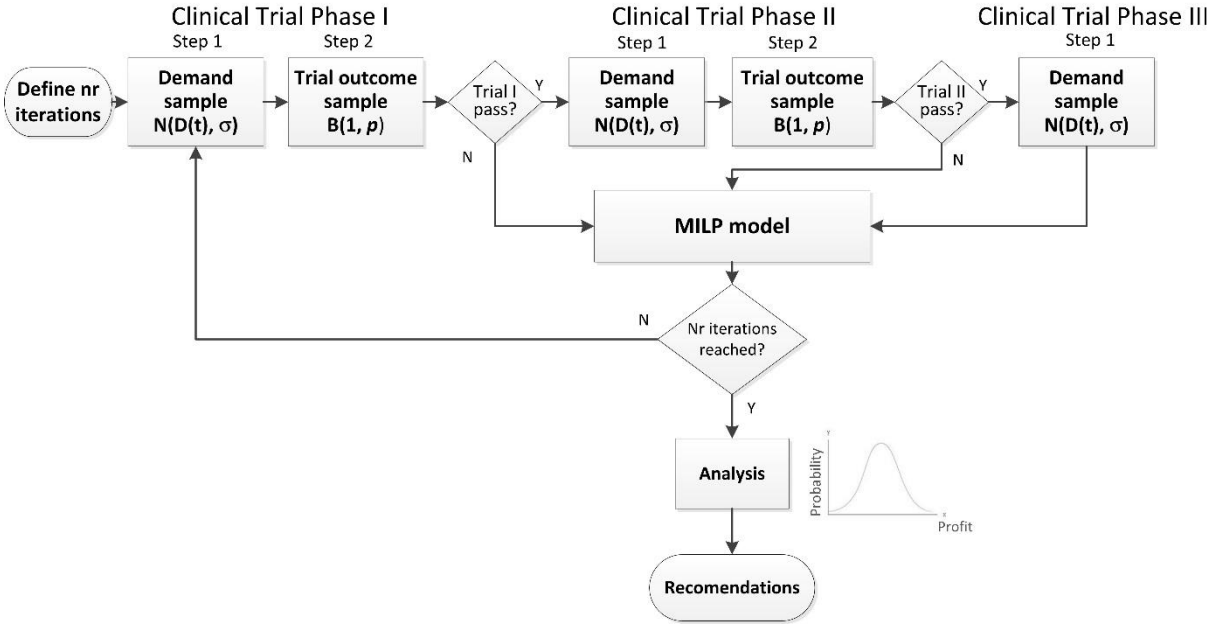

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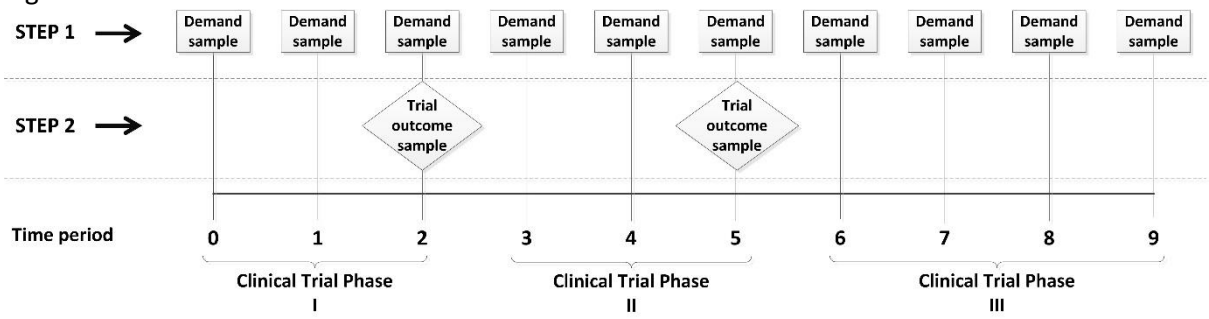

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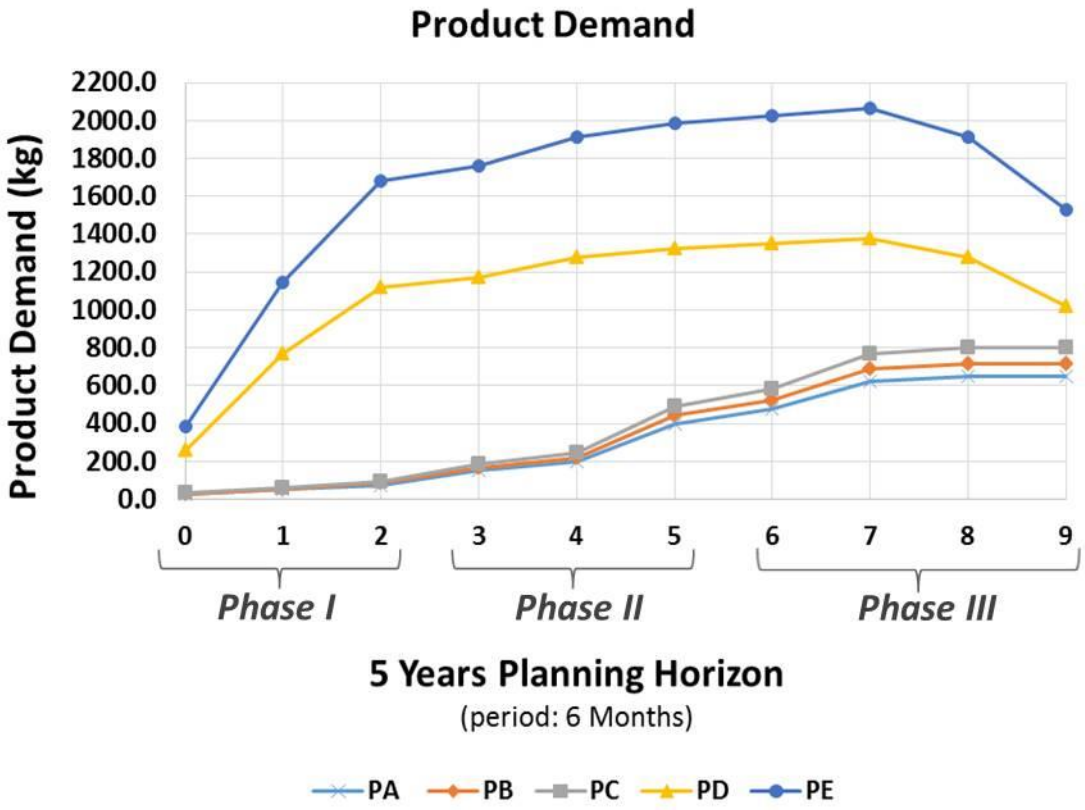

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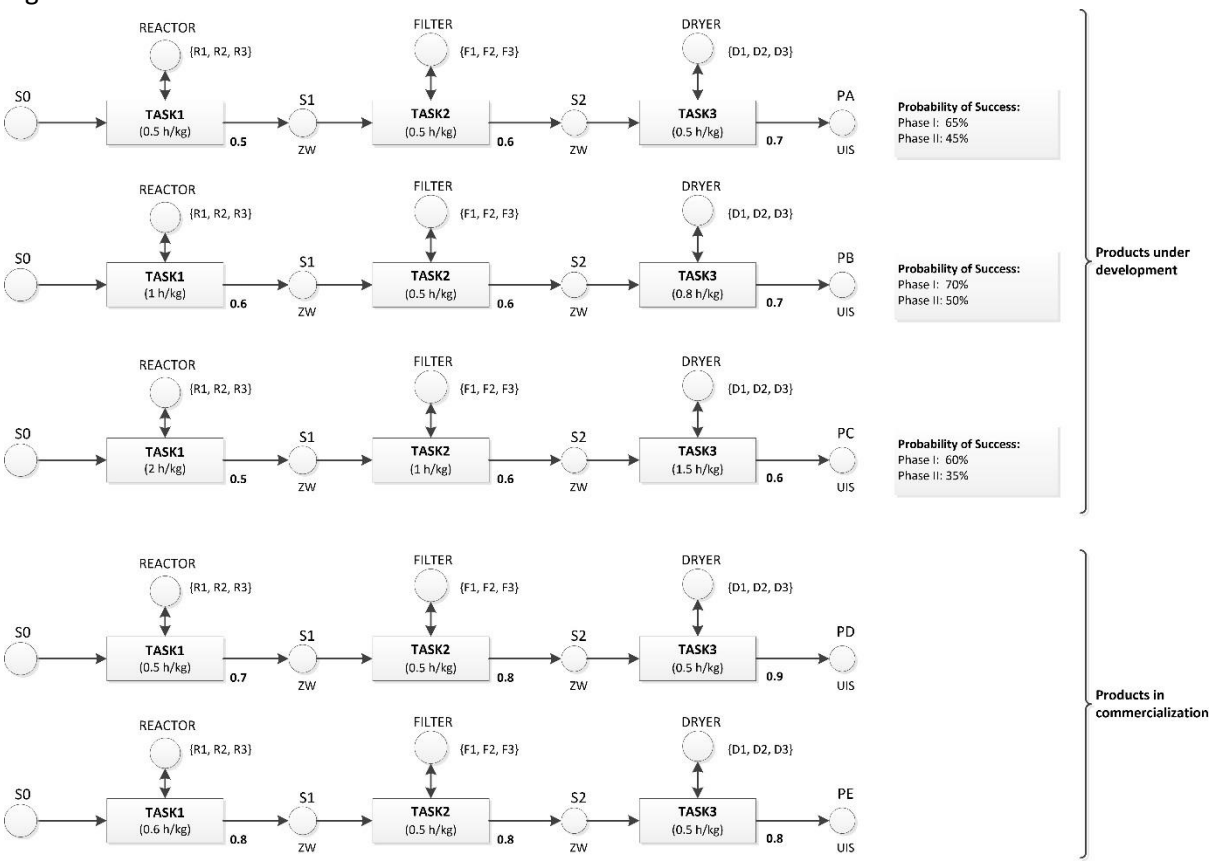

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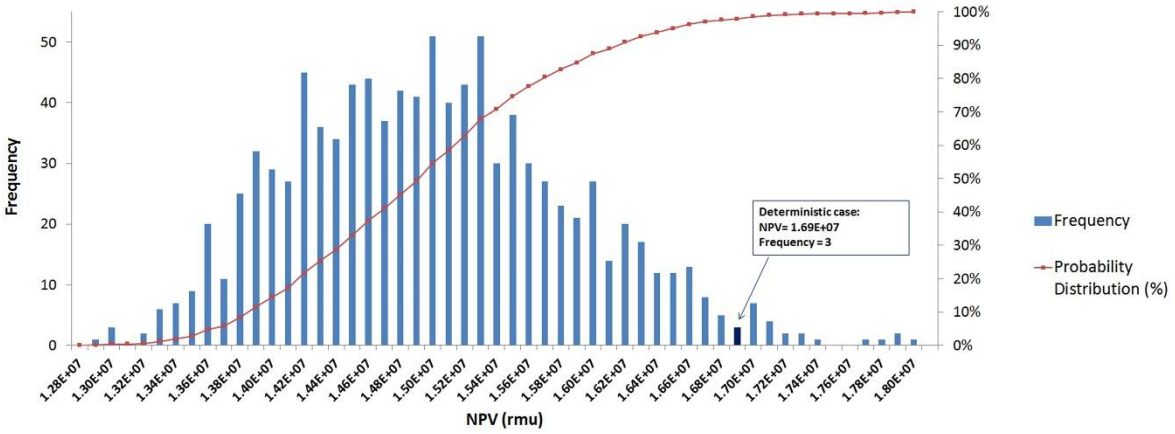

Table 2. Deterministic process design results for the under development products

	Product PA		Product PB		Product PC	
	t	**Process**	**t**	**Process**	**t**	**Process**
Phase I	**0**	D1L2_F1L2_R1L2	**0**	D1L4_F2L4_R1L4_R2L4	**0**	D1L1_F1L1_R1L1
	1	D1L2_F1L2_R1L2	**1**	D1L4_F3L4_R1L4	**1**	D1L1_F1L1_R1L1
	2	D1L2_F1L2_R1L2	**2**	-	**2**	D1L1_F1L1_R1L1
Phase II	**3**	D1L4_F1L4_R1L4	**3**	D2L4_F2L4_R1L4	**3**	D1L1_F1L1_R1L1_R2L1
	4	D1L4_F1L4_R1L4	**4**	D2L4_F2L4_R1L4	**4**	D2L1_F1L1_R1L1_R2L1
	5	D1L4_F1L4_R1L4_R2L4	**5**	D2L4_F1L4_F2L4_R1L4	**5**	D2L1_F2L1_R1L1_R2L1
Phase III	**6**	D1L4_F1L4_R1L4_R2L4_R3L4	**6**	D1L4_F1L4_F2L4_R1L4_R2L4	**6**	D2L1_F2L1_R1L1_R2L1
	7	D1L4_F1L4_R1L4_R2L4_R3L4	**7**	D1L4_F1L4_F2L4_R1L4_R2L4	**7**	D2L2_F2L2_R1L2_R3L2
	8	D1L4_F1L4_R1L4_R2L4_R3L4	**8**	D1L4_F1L4_F2L4_R1L4	**8**	D2L2_F2L2_R1L2_R2L2
	9	D1L4_F1L4_R1L4_R2L4	**9**	D1L4_F1L4_R1L4	**9**	D2L2_F2L2_R2L2