Recent Trends and Challenges in Planning and Scheduling of Chemical-Pharmaceutical Plants

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Abstract. This paper discusses the current trends in optimization methods for solving planning and scheduling problems in the chemical-pharmaceutical industry. The challenges of this industry and the recent advances in modeling these problems show that optimization methods need to provide highly integrated solutions encompassing decision-making at both R&D and Operations levels. The heterogeneous demand, characteristic of the complex drug development cycle, asks for mixed planning strategies capable of increasing the resources utilization and the plant output, and of dealing with uncertainty.

1 Introduction

Industrial companies are continuously assessing their operations, as a way to increase the overall effectiveness of production systems. Markets where these organizations operate tend to become more complex over time, forcing companies to increase their responsiveness, both in terms of time and cost. The case of the pharmaceutical industry is a good example on how market is driving the change of the drug development cycle and manufacturing activities. Some of the most relevant driving factors are related to: a) the drought in new drug approval applications by the regulatory agencies; b) the uncertainty associated to the Research and Development (R&D) activities and trials I-III phases; and c) the pressure on the drug prices and demand variability, caused by patent drops. This context is putting enormous pressure in the industry to reduce the time and the cost required to launch new drugs to market and, when drugs are being commercialized, to reduce the manufacturing and inventory costs and the typically long production lead times [1]. The planning and scheduling functions are then critical in these highly dynamic production systems.

The relevance of using optimization tools to solve planning and scheduling problems has been recognized by the industry [2]. Thus, not surprisingly, the efforts made in the past years, by academia and industry, resulted into several successful cases of integration of optimization tools into complex decision-making

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processes related to supply chain, process design, planning and scheduling [3]. However, despite the significant progress achieved in modeling these problems, the development of efficient optimization and solution methods, capable to be integrated in corporate decision-making, is still an open research topic. This paper describes the major issues in planning and scheduling decision-making in the chemical-pharmaceutical industry, and reviews some important optimization methods that have been applied in this context. The remainder of the paper is structured as follows. Section 2 presents some recent trends in modeling planning and scheduling problems in the case of the chemical-pharmaceutical industry. The characteristics of this industry are described so as to provide a common understanding of the several complexities associated with planning and scheduling problems. Section 3 summarizes the challenges and opportunities in this field. Finally, in section 4, some concluding remarks are presented.

2 Planning and Scheduling Decision-Making

Manufacturers and regulators in the pharmaceutical industry create a specific context for Operations Management [4], thus conditioning planning and scheduling functions. The planning problem involves the determination of tactical production plans, in which decisions are typically made assuming a certain degree of aggregation of resources and time, hence imposing bounds to the scheduling problem. The scheduling problem involves the determination of operational plans at the level of the most elementary production resources and at a fine time grid. In practice both problems may present several conflicting objectives such as, for example, minimizing costs and minimizing delivery times. Moreover the characteristics of the market, of production processes, and of chemical plants make planning and scheduling tasks particularly difficult to perform [5].

The drug development cycle imposes the coordination of a large number of different R&D and manufacturing activities, and therefore planning and scheduling decision-making is essential to achieve a global optimization of these systems. In this context, solving planning and scheduling problems requires the application of different methods that are briefly presented next (due to space limitations, we do not to provide here an extensive review on this topic):

Planning and Scheduling of Products under Development

The planning and scheduling functions are deeply coupled with R&D tasks (Fig. 1). Process Design consists in using the information available to develop an industrial process. Here, the characteristics of the products and processing units are considered in developing an efficient production process concerning the resources utilization, given a set of market and operating constraints. And Production Execution and Control involve production dispatching, control and quality assessment, among other activities.

Planning and scheduling encompass then the coordination of development and manufacturing activities, so as to move from the laboratory scale to the industrial scale, this resulting in the determination of the final product quantities (lot sizes) and in a first assessment of the processing times. The goal is to find optimal schedules that maximize the expected economic value of the investment by considering the resources availability, the probability of success of the clinical trials, and the associated costs. Varma et al. [6] have developed a comprehensive decision-making framework called Sim-Opt for resource management, that includes components for stochastic simulation, schedules generation based on a mixed integer linear programming (MILP) formulation, and evaluation of various resource strategies. A common modeling method for solving the clinical trials planning problem is multi-stage stochastic programing, coupled with solution methods, such as specialized branch and cut algorithms, Lagrangean decomposition, Benders decomposition, as a way to improve the computational performance [7,8].

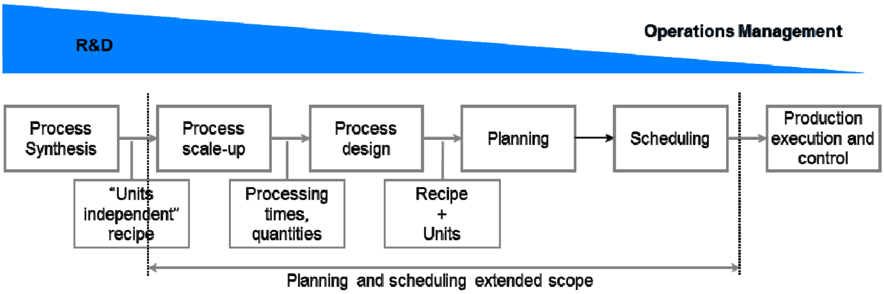

Fig. 1 Scope of the planning and scheduling problems. Source [5]

Integration of Planning and Scheduling

It is common to find chemical plants that manufacture products with dissimilar production recipes and volumes. For low volume production (short-term mode) a reduced number of batches are produced and for high volume production (campaign mode) the number and size of batches tends to be higher. These strategies have impact on how resources are allocated and on the system responsiveness. The short-term mode, under a multipurpose environment, requires a higher responsiveness from the production system, since resources are shared between several products in a very dynamic production environment, whereas in the campaign mode, resources are allocated to single products during long time periods. Campaign schedules can be computed using a periodic scheduling approach [9], leading to schedules that are seen as operationally easier to manage and execute. The combination of both planning modes (short/campaign) is often present when a mixed planning strategy is explored. In these cases short-term demand can often be planned to follow a non-periodic scheduling, and campaigns are generated to follow a periodic scheduling [10]. Alternatively, planning and scheduling problems have been simultaneously solved using multiscale methods. These methods account for the impact of the mid-term decisions in the short-term decisions (and vice-versa) and integrate the decision-making processes of different planning levels [11,12]. Multiscale methods propose decomposition schemes that include models with different planning horizons and different aggregation levels for the associated problems, and aim at increasing the resources utilization and the facility output [13]. So relevant data for decision-making is modeled with different time scales depending on its availability and reliability.

Finally, a reference should be made to the integration of planning and scheduling with real time optimization/control, in order to improve the performance of the production systems at all hierarchical decision-making levels [14].

Production Simulation-Optimization

Modeling the uncertainty of real world problems with optimization often results into models with a large number of variables, that are computationally intractable. On the other hand, simulation can easily deal with the stochastic nature of the problems and with complicating constraints of the production systems. Recent approaches combine simulation and optimization in new, efficient solution methods. Simulation can be used to assess solutions provided by deterministic optimization models, by considering the uncertainty of parameters, and by providing additional information to optimization models. Chen et al. [15] developed a simulation-optimization model for managing the entire trial supply chain, including the planning and scheduling of Active Pharmaceutical Ingredients (API) manufacturing. Sahay, Ierapetritou [16] have applied an agent-based model hybridized with a linear programing model, to study different supply chain decision-making policies. Eberle et al. [17] have applied a Monte-Carlo simulation to estimate the production lead time of pharmaceutical processes.

Ontologies and Knowledge Management

Models to support planning and scheduling decisions are part of complex software environments that tend to share data structures and that involve many information flows. Zhao et al. [18] introduced a web-based infrastructure called *Pharmaceutical Informatics* that aims at supporting the overall decision-making process and includes the following areas: product portfolio, capacity planning, planning and scheduling, process control and safety, and supply chain management. Muñoz et al. [19] proposed an ontological framework for streamlining the exchange of information and knowledge models between different applications and hierarchical decision levels. The framework has been demonstrated in a supply chain network design-planning problem. Focusing on solving the scheduling problem, Moniz et al. [20] proposed a methodology that integrates the representation of the scheduling problem, the optimization model, and the decision-making process. The input data required for the MILP they have developed is automatically captured by a novel process representation tool used by several departments of the company.

3 Challenges and Opportunities

Despite the significant academic and industrial achievements in this area, there are relevant challenges that make planning and scheduling decision-making particularly difficult to address. Solving the integrated problem requires the development of comprehensive optimization tools that should be integrated with upstream design decisions and with downstream process control, in order to deal with the complex tradeoffs between development and manufacturing. In fact, understanding and modeling the conditions for achieving the global optimization of these manufacturing systems is by itself a quite hard task. To address this issue, we have proposed in a previous work, a representation of R&D and manufacturing tradeoffs, called Delivery Trade-offs Matrix (DTM) (**Fig. 2 a**) [5]. The DTM shows the three phases of the drug development cycle (R&D, trials I-III, and commercialization) against some relevant issues this industry needs to continuously manage, such as cost, uncertainty, time-to-market, amount delivered, campaign and short-term planning. The size of the "bubble" at each phase is proportional to the lot size, showing that a batch plant may need to produce from few grams to hundred kilos of the same product.

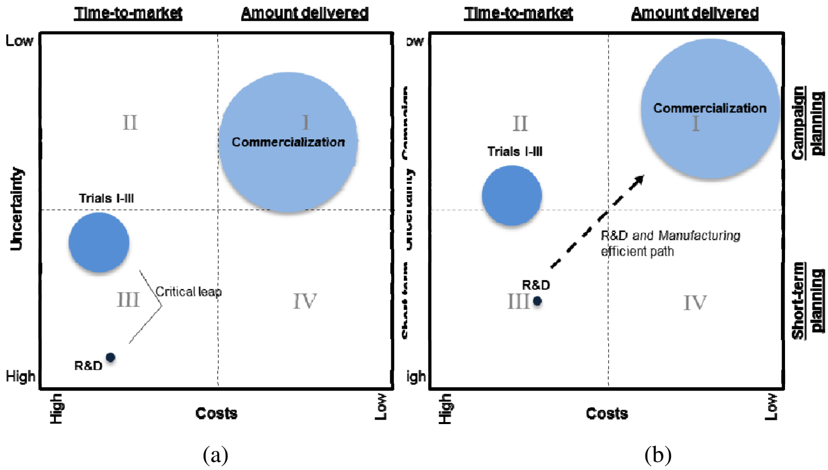

Fig. 2 Delivery Trade-offs Matrix (DTM) of the pharmaceutical industry: a) current state, b) future scenario. Source [5]

Several different process scale-ups are typically performed to respond to the demands at the early stages of the development, at the clinical trials I-III, and also after the drug approval for commercialization. Therefore the development of methods capable of addressing the long–term dimension of the scale-up decisions is surely a promising topic of research. The delivery of drugs for Trials I-III is of extreme importance, due to the fact that the clinical trials must be rigorously followed, and also because it is common to have more than one company developing similar drugs, time-to-market being therefore essential (Fig. 2 a). On the other hand, after launching the drug in the market there is more flexibility concerning delivery dates, since typically there are more inventory on the supply chain [21]. So, while in the R&D and trials I-III phases, time-to-market is the main driver, in the commercialization phase delivering the right product amounts appears to be more relevant.

In this industry, probably more than in other sectors, the product is strongly linked to the process. The way chemical processes are designed, implemented, controlled, and scaled-up strongly determines the overall cost and quality of the product, the total production time, and the global efficiency of the multipurpose batch plant. So, it is interesting to extend the scope of the planning and scheduling functions to account for design problems [22]. This is especially useful when manufacturing involves chemical processes that are under development. The solution space of planning and scheduling decisions will benefit with the integration of scale-up and process design decisions, and will potentially lead to a better utilization of the available resources, thus increasing the plant output. In general, the integration of models for the different decision levels still needs to be improved, to avoid suboptimal solutions and to better represent the real information flow of the decision making process.

Uncertainty and costs are quite complex to deal with, since the knowledge at the R&D phase is seldom sufficient to ensure a successful scale up to the plant [1]. For example, the allocation of the production resources to the development and manufacturing of APIs is done 6 to 12 months in advance, and therefore changes in the plans may have a significant impact in the manufacturing costs and delivery time. Demand fluctuations occur since the first scale up from the laboratory scale to the plant scale, and also during the commercialization phase. Moreover, other sources of uncertainty such as uncertainty on complex steps of the production process, processing times, yields, machine breakdowns, and changeover times need to be modeled with the different spatial and time scales. In fact capturing all relevant sources of uncertainty in a comprehensive framework for supporting the planning and scheduling decision-making process is not yet a solved question. Simulation-optimization can, in this context, provide interesting approaches to combine the stochastic and deterministic parameters of the planning and scheduling problems.

It should also be emphasized that multipurpose batch plants run in short-term mode to fulfil a small product demand (*e.g.* supply clinical trials), or run preferably in campaign mode to respond to a regular demand. In practice, many multipurpose batch plants simultaneously produce both types of products [20], however a reduced number of research works propose solution methods capable of addressing mixed planning strategies.

The complexity and variety of the decisions that need to be made during a drug development cycle require highly integrated information flows. We can therefore expect that the development of ontologies for building comprehensive frameworks will foster the integration of model-based applications by this industry. The chemical-pharmaceutical industry has to systematically address the huge uncertainty present in the supply chain in order to decrease the development and manufacturing time and cost (Fig. 2 b). The path to efficient R&D and manufacturing activities requires integrated decision-making and multiscale modeling so as to account with a rather heterogeneous demand.

4 Conclusions

This paper discusses some current trends in optimization methods for solving planning and scheduling problems in the chemical-pharmaceutical industry. Recent research works address integration, uncertainty, knowledge management and modeling issues, to solve extended planning and scheduling problems. Some of these works propose methods for solving real world problems and show the benefits of the deployment of model-based applications in the industry. In fact the need for innovative, integrated solution approaches is also justified by the pressure to reduce R&D and manufacturing time and costs but, despite the significant academic and industrial achievements in this area, there are still quite relevant challenges to address.

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References

1. Federsel, H.-J.: Chemical Process Research and Development in the 21st Century: Challenges, Strategies, and Solutions from a Pharmaceutical Industry Perspective. Accounts of Chemical Research 42(5), 671–680 (2009). doi:10.1021/ar800257v
2. Klatt, K.-U., Marquardt, W.: Perspectives for process systems engineering—Personal views from academia and industry. Comput. Chem. Eng. 33(3), 536–550 (2009)
3. Grossmann, I.: Enterprise-wide optimization: A new frontier in process systems engineering. AIChE Journal 51(7), 1846–1857 (2005)
4. Laínez, J.M., Schaefer, E., Reklaitis, G.V.: Challenges and opportunities in enterprise-wide optimization in the pharmaceutical industry. Comput. Chem. Eng. 47, 19–28 (2012)
5. Moniz, S., Barbosa Póvoa, A.P., Pinho de Sousa, J.: On the complexity of production planning and scheduling in the pharmaceutical industry: the Delivery Trade-offs Matrix. Computer Aided Chemical Engineering 37, 1865–1870 (2015)
6. Varma, V.A., Pekny, J.F., Blau, G.E., Reklaitis, G.V.: A framework for addressing stochastic and combinatorial aspects of scheduling and resource allocation in pharmaceutical R&D pipelines. Comput. Chem. Eng. 32(4), 1000–1015 (2008)
7. Colvin, M., Maravelias, C.T.: Modeling methods and a branch and cut algorithm for pharmaceutical clinical trial planning using stochastic programming. European Journal of Operational Research 203(1), 205–215 (2010)
8. Sundaramoorthy, A., Li, X., Evans, J.M., Barton, P.I.: Capacity planning under clinical trials uncertainty in continuous pharmaceutical manufacturing, 2: solution method. Industrial & Engineering Chemistry Research 51(42), 13703–13711 (2012)

9. Shah, N., Pantelides, C., Sargent, R.: Optimal periodic scheduling of multipurpose batch plants. Annals of Operations Research 42(1), 193–228 (1993)
10. Moniz, S., Barbosa-Póvoa, A.P., Pinho de Sousa, J.: Simultaneous regular and non-regular production scheduling of multipurpose batch plants: A real chemical–pharmaceutical case study. Comput. Chem. Eng. 67, 83–102 (2014)
11. Stefansson, H., Shah, N., Jensson, P.: Multiscale planning and scheduling in the secondary pharmaceutical industry. AIChE Journal 52(12), 4133–4149 (2006)
12. Amaro, A., Barbosa-Póvoa, A.: Planning and scheduling of industrial supply chains with reverse flows: A real pharmaceutical case study. Comput. Chem. Eng. 32(11), 2606–2625 (2008)
13. Maravelias, C.T., Sung, C.: Integration of production planning and scheduling: Overview, challenges and opportunities. Comput. Chem. Eng. 33(12), 1919–1930 (2009)
14. Chu, Y., You, F.: Model-based integration of control and operations: Overview, challenges, advances, and opportunities. Comput. Chem. Eng. (2015)
15. Chen, Y., Mockus, L., Orcun, S., Reklaitis, G.V.: Simulation-optimization approach to clinical trial supply chain management with demand scenario forecast. Comput. Chem. Eng. 40, 82–96 (2012)
16. Sahay, N., Ierapetritou, M.: Hybrid Simulation Based Optimization Framework for Centralized and Decentralized Supply Chains. Industrial & Engineering Chemistry Research 53(10), 3996–4007 (2014)
17. Eberle, L.G., Sugiyama, H., Schmidt, R.: Improving lead time of pharmaceutical production processes using Monte Carlo simulation. Comput. Chem. Eng. 68, 255–263 (2014)
18. Zhao, C., Joglekar, G., Jain, A., Venkatasubramanian, V., Reklaitis, G.: Pharmaceutical informatics: A novel paradigm for pharmaceutical product development and manufacture. Computer Aided Chemical Engineering 20, 1561–1566 (2005)
19. Muñoz, E., Capón-García, E., Laínez, J.M., Espuña, A., Puigjaner, L.: Integration of enterprise levels based on an ontological framework. Chemical Engineering Research and Design (2013)
20. Moniz, S., Barbosa-Póvoa, A.P., Pinho de Sousa, J., Duarte, P.: A solution methodology for scheduling problems in batch plants. Industrial & Engineering Chemistry Research (2014). doi:10.1021/ie403129y
21. Shah, N.: Pharmaceutical supply chains: key issues and strategies for optimisation. Comput. Chem. Eng. 28(6-7), 929–941 (2004)
22. Barbosa-Povoa, A.P.: A critical review on the design and retrofit of batch plants. Comput. Chem. Eng. 31(7), 833–855 (2007). doi:10.1016/j.compchemeng.2006.08.003