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On the complexity of production planning and scheduling in the pharmaceutical industry: the Delivery Trade-offs Matrix

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Abstract

The manufacturing of pharmaceutical products is preceded by complex development phases where process design, planning, and scheduling problems must be considered as deeply linked, fact that has not yet been adequately handled by the existing literature. In this perspective, this work discusses the role of the production planning and scheduling decisions in the pharmaceutical industry. It starts by analysing the main aspects that influence planning and scheduling, and defines an extended scope of the related problems, as a way to account for higher levels of integration between process design and operational decisions. We propose a novel conceptual representation, the *Delivery Trade-offs Matrix* (DTM) to help managing the trade-offs occurring in the drug development process and to expose the factors that affect the performance of these manufacturing systems.

Keywords: Planning; scheduling; pharmaceutical industry

1. Introduction

The pharmaceutical industry can be viewed as a complex system of processes, operations, and organizations involved in the discovery, development, and manufacturing of drugs. Companies operating in this industry are responsible for: a) research and development (R&D) activities; b) development and manufacturing of active pharmaceutical ingredients (APIs); and c) drugs manufacturing. Federsel (2009) recognized that, although the pharmaceutical industry has historically tolerated total time investments of more than 10 years from idea to market, the current worldwide paradigm imposes a significant reduction of this time. The pharmaceutical industry is therefore confronted with several challenges that are related to increasing R&D costs, long cycle times, and low probabilities of success (Hynes III, 2009). Additionally, over the years, manufacturers and regulators have created an environment for operations management that strongly conditions the planning and scheduling functions. In this work, we have looked into the literature addressing planning and scheduling problems in the sector, and tried to derive some general principles for defining and extending the scope of these functions, and to identify some current and future research and industrial challenges.

The rest of the paper is structured as follows. Section 2 presents the critical factors that determine how planning and scheduling are done in the pharmaceutical industry.

Section 3 discusses the planning and scheduling functions and proposes an extension of the scope for the related problems, to account for higher levels of integration between process design and operational decisions. In section 4, the *Delivery Trade-offs Matrix (DTM)* is introduced. Finally, in section 5, some concluding remarks are presented.

2. Critical factors for planning and scheduling

Planning and scheduling are functions that primarily aim at reducing costs and improving responsiveness of the manufacturing systems. One recent review on planning and scheduling has been written by Harjunkoski et al., (2013). The critical factors that drive the planning and scheduling functions, in the particular context of the pharmaceutical industry, can be grouped in three categories: market, processes, and plants. Market factors are related to the specific contextual factors of this industry. Process factors have to do with the structure of the chemical processes. Plant factors relate to the operating strategies and resources characteristics of the manufacturing systems. Note that some of the process and plant characteristics discussed in the following subsections are more general and not specific to the pharmaceutical industry.

2.1. Market

The market context has a direct influence on the planning and scheduling functions. First of all the pharmaceutical market is highly fragmented. There is a large variability on the demand, that is also a result of the pressure created by generic drugs, and that leads to larger production mixes in the manufacturing sites. Operations flexibility is therefore required to fit the systems to this heterogeneous demand, and for that reason efficient planning and scheduling methods are required. Manufacturing in a high regulated market has to deal with additional complexities that do not exist in less regulated markets. In fact chemical processes are executed under a close supervision of the regulatory agencies that define rigorous procedures to monitor process changes. Globally, the time-to-market issue and the pressure to reduce costs are imposing operations to run more efficiently and therefore advanced planning and scheduling methods are necessary (Moniz et al., 2014).

2.2. Processes

The production process topology strongly determines the scheduling models that can be applied. The work of Mendez et al. (2006) provides a comprehensive review on the different types of scheduling models. In the manufacturing of APIs, for example, processes require numerous production steps with tasks having short and long processing times, usually spanning across several working shifts. Regulatory and quality procedures define the *lot size* and the *changeover* requirements that must be rigorously followed in the manufacturing sites, thus introducing additional time to the effective production time. Stable intermediaries and final products are produced in lots, and therefore lots traceability must be ensured. The first batches after a *scale-up* are usually more difficult to produce, since this may involve the use of different processing units or even performing changes in the process. For that reason, these processes impose frequent revisions of the production schedule.

2.3. Plants

The plant structure has also implications on how planning and scheduling are performed. Note that, although the modelling approach strongly depends on the process topology (as discussed above), the characteristics of the plants (such as resources, plant structure, operating mode, and batch/continuous manufacturing) lead as well to specific

planning and scheduling problems. Continuous manufacturing of pharmaceuticals is an emergent process mode that relies on flow reactors and is currently being evaluated for the production of drugs. A consequence of using flow reactors, instead of batch reactors, is that the production process moves from a batch mode to continuous operating conditions (Buchholz, 2010). Finally, it is important to mention that for aiming the full operational efficiency the integration with advanced control systems should be performed. However, here there are significant practical and theoretical integration challenges, Engell and Harjunkoski (2012).

3. Extending the scope of planning and scheduling problems

In the context of process development and manufacturing of drugs, R&D, and Operations Management (OM) departments perform critical activities that determine how planning and scheduling are effectively done (see Figure 1).

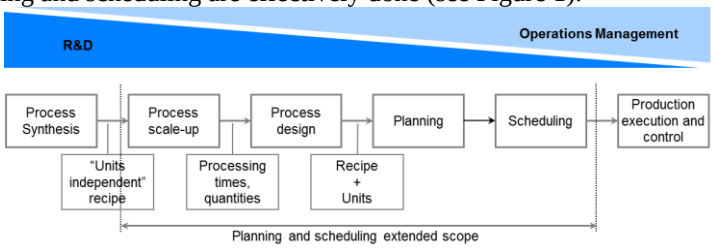

Figure 1 – Scope of the planning and scheduling problems.

We argue that the planning and scheduling functions must be extended in order to integrate decisions made in the *process scale-up* and *design* steps. The planning process, whether long-term or short-term, will clearly benefit from considering decisions taken at the scale-up and process design levels, as these decisions have a direct impact on the determination of the processing units suitable for the process, this leading to different production routes (alternative processes). On the contrary, after schedules have been released to the shop-floor, changes on planning and scheduling decisions can only be very limited, although *rescheduling* is a common practice. The same happens with changes in process design decisions that may not be possible or are not desirable to perform. In summary, we propose that the scope of the planning and scheduling functions is extended to account for design decisions (Barbosa-Povoa (2007)), especially for chemical manufacturing processes that are under development. This will increase the solution space of planning and scheduling decisions, hopefully leading to more globally optimized operations.

4. The Delivery Trade-offs Matrix

The ultimate goal of planning and scheduling is to deliver the right amounts of product at the right time, cost, and quality. Thus, in order to provide guidance on the issues that determine the effectiveness of manufacturing a new drug to the market, we propose a conceptual representation, named the *Delivery Trade-offs Matrix* (DTM) that is depicted in Figure 2. The relative importance of *costs* and *uncertainty* on the manufacturing activities that support the development and delivery of APIs or final products can be assessed in the DTM. It is important to notice that the proposed DTMs were built taking into account a set of estimated values available in the literature. To the best of our knowledge, there are no reliable figures regarding the cost structure and uncertainty associated to the R&D, trials I-III, and commercialization phases. However, the huge development and manufacturing costs in the pharmaceutical industry clearly justify a discussion on the path to follow towards manufacturing efficiency.

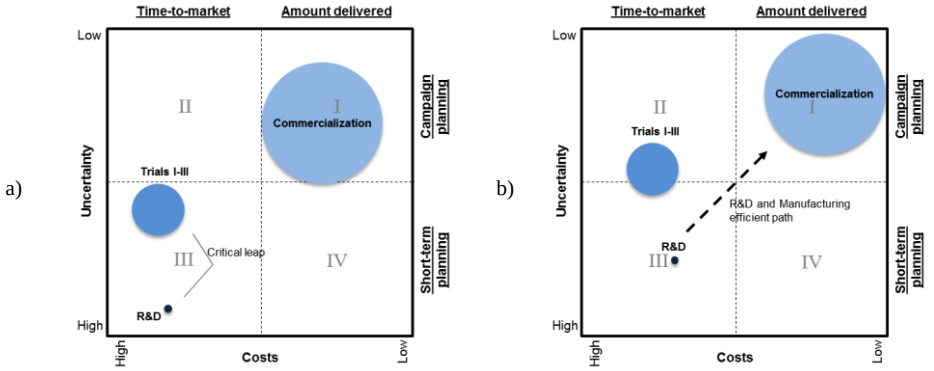

Figure 2 – Delivery Trade-offs Matrix (DTM) of the pharmaceutical industry: a) current state, b) future scenario.

The matrix depicts three phases of the drug development cycle (R&D, trials I-III, and commercialization). The R&D phase accounts for discovery, safety, and toxicology research activities and clinical supplies. Trials I-III relate to clinical studies performed on humans. The commercialization phase includes the manufacturing activities required to deliver the right amounts of product to the market, after approval by the regulatory agencies. Uncertainty and costs are represented in a continuous scale from *high* to *low*. The proportion of the production lot size at each phase is indicated by the size of the associated bubble. The DTM of Figure 2.a) shows the current trade-offs of the industry, while b) depicts a future scenario, as a possible response to the challenges the pharmaceutical industry is facing and needs to overcome. These aspects are next discussed in more detail.

4.1. Uncertainty and costs

At the start of a research program, products and processes have not yet been developed, and therefore there is a high uncertainty associated to the drug structure and to the production process. Uncertainty makes planning decisions more complex, since it is more difficult to estimate the required times and resources. For example, in the development and manufacturing of APIs it is common to allocate production resources 6 to 12 months in advance. Thus, changes in the plans may have a significant impact in manufacturing costs and delivery time. With drug development the uncertainty tends to decrease as product and process characteristics are better understood. In fact at the laboratory scale, only small amounts are produced (around few hundred grams). The delivery of the first scaled up batch (usually between 1 to 5 kg), used to support toxicological and formulation studies, along with phase I trials, is on the critical path of the development process This scale-up is particular difficult to perform since the knowledge obtained at the laboratory scale is seldom sufficient to guarantee a successful process at a plant scale (Federsel, 2009). Moreover, the drug development process requires a series of scale-ups so as to develop an efficient production process.

At the commercialization stage, the need for API or drug products is normally in the order of hundreds of kilograms. The processes are well defined, thus the uncertainty is mainly associated to market parameters such as demand, and to the processing time of the complex production tasks. The current practice demonstrates that there are large costs and high uncertainty at the R&D and trials I-III phases (see Figure 2 a), with the total estimated cost of bringing a new drug to market being larger than 1 billion dollars (Kessel, 2011). In terms of the total cost structure, pharmaceutical R&D costs are

around 30% to 35%, and clinical trials (typically representing the most significant cost) can be between 35% to 40% of the total (Suresh & Basu, 2008).

4.2. Time-to-market and amount delivered

It should be noted that from the planning and scheduling perspective, the delivery of products to Trials I-III phases is of extreme importance. Shah (2004) and Buchholz (2010) pointed out that time-to-market is a critical driver of the pharmaceutical industry. Additionally, Buchholz (2010) highlighted that fast and robust scalability of the production processes is another relevant driver for this industry. In fact it is quite often to have more than one company developing similar drugs, and therefore the importance to respect due dates is even more crucial.

On the other hand, at the commercialization phase there is more flexibility concerning delivery dates, if there is inventory on the supply chain. According to Shah (2004), the whole pharmaceutical chain stock can represent 30% to 90% of the annual demand in quantity. Therefore, at this phase, we can say that delivering the right product amounts is relatively more important than respecting delivery dates. Remember that the production lot sizes at the Trials I-III phases are in the order of few kilograms, while after several scale-up and validation steps, the lot sizes are around hundreds of kilograms. After drug development, the manufacturing costs are lower and tend to decrease with the reduction of the root causes of variability in the production process.
Concerning the operating mode, manufacturing sites run in *short-term mode* to fulfil a small product demand, or run preferably in *campaign mode* to respond to a regular demand. Sometimes the short-term mode is also used for manufacturing products that are in commercialization, this naturally resulting in the production of a smaller number of lots. However, in all cases the process must run with the same lot size as approved by the regulatory agencies.

4.3. The path to efficient R&D and manufacturing activities

All the above issues led the pharmaceutical industry to recognize the need for reducing time-to-market, the costs of new drug development, and the manufacturing costs. The path to efficient R&D and manufacturing activities requires new ways to address uncertainty and reduce costs (see Figure 2 b). This will involve the introduction of new production technologies (Suresh & Basu, 2008), as well as the adoption of innovative process design, planning, and scheduling decision-making tools. For example, according to Roberge et al. (2005), 50% of the reaction tasks in the chemical-pharmaceutical industry could benefit from the adoption of continuous processes based on the micro-reactor technology. In what concerns decision-making, the relevance of applying optimization tools and deploying more integrated decision-making processes is being recognized by the industry, despite the challenges that still exist (Grossmann, 2012). A new path must then be followed as represented in Figure 2 b. Such path must focus on improving the reliability of the drugs delivery by dealing with the uncertainty and the associated costs. The challenge here is to address in a systematic way the huge uncertainty present in the supply chain, so as to decrease the delivery times and meet the delivery quantities, thus improving the delivery reliability and response time. In the manufacturing sites, a more effective utilization of the resources can be achieved by integrating process design, planning and scheduling decisions and reducing the production lot sizes, but without increasing the costs, particularly the ones related to the long production changeovers.

5. Conclusions

This work analyses the main aspects that influence planning and scheduling decisions in the context of the pharmaceutical industry. Extending the traditional scope of planning and scheduling functions is particularly interesting, if drug development and manufacturing activities are simultaneously considered. The critical factors that determine planning and scheduling were identified and grouped in three categories: market, processes, and plants. In our view, comprehensive optimization methods for this sector must take into account these factors. Finally, we propose a conceptual representation, the Delivery Trade-offs Matrix, as a contribution to better managing uncertainty and costs issues, in the drug development and manufacturing activities. The matrix shows that the pharmaceutical industry should focus on the manufacturing and delivery issues knowing that each phase of the development cycle has different challenges. The integration of design decisions in the planning and scheduling is fundamental to do in the early stages of the drug development cycle. While the implementation of high flexible and high efficient manufacturing systems will then require the integration of planning and scheduling and control, especially during the commercialization phase.

References

A. Barbosa-Povoa, 2007, A critical review on the design and retrofit of batch plants, Computers & Chemical Engineering, 31, 833-855

S. Buchholz, 2010, Future manufacturing approaches in the chemical and pharmaceutical industry, Chemical Engineering and Processing: Process Intensification, 49, 993-995

S. Engell, I. Harjunkoski, 2012, Optimal operation: Scheduling, advanced control and their integration, Computers & Chemical Engineering

H. Federsel, 2009, Chemical Process Research and Development in the 21st Century: Challenges, Strategies, and Solutions from a Pharmaceutical Industry Perspective, Accounts of Chemical Research, 42, 671-680

I. Grossmann, 2012, Advances in mathematical programming models for enterprise-wide optimization, Computers & Chemical Engineering

I. Harjunkoski, C. Maravelias, P. Bongers, P. Castro, S. Engell, I. Grossmann, J. Hooker, C. Méndez, G. Sand, J. Wassick, Scope for industrial applications of production scheduling models and solution methods, Computers & Chemical Engineering, Volume 62, 5 March 2014, Pages 161-193

M. Hynes III, 2009, Project and capacity management: An application to drug development, Computers & Chemical Engineering, 33, 1994-1998

M. Kessel, M, 2011, The problems with today's pharmaceutical business an outsider's view, Nature biotechnology, 29, 27-33

C. Mendez, J. Cerda, I. Grossmann, I. Harjunkoski, M. Fahl, 2006, State-of-the-art review of optimization methods for short-term scheduling of batch processes, Computers & Chemical Engineering, 30, 913-946

S. Moniz, A. Barbosa-Póvoa, J. Sousa, P. Duarte, 2014, A solution methodology for scheduling problems in batch plants, Industrial & engineering chemistry research

D. Roberge, L. Ducry, N. Bieler, P. Cretton, B. Zimmermann, 2005, Microreactor technology: a revolution for the fine chemical and pharmaceutical industries, Chemical engineering & technology, 28, 318-323

N. Shah, 2004, Pharmaceutical supply chains: key issues and strategies for optimisation, Computers & Chemical Engineering, 28, 929-941

P. Suresh, P. Basu, 2008, Improving pharmaceutical product development and manufacturing: impact on cost of drug development and cost of goods sold of pharmaceuticals, Journal of Pharmaceutical Innovation, 3, 175-187