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Improving lead time of pharmaceutical production processes using Monte Carlo simulation☆

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ABSTRACT

Reliable product supply is one of the most critical missions of the pharmaceutical industry. The lead time, i.e. the duration between start and end of an activity, needs to be well managed in any production facility in order to make scheduling predictable, agile and flexible. We present a method for measuring and improving production lead time of pharmaceutical processes with a primary focus on Parenterals (i.e. injectables) production processes. Monte Carlo simulation is applied for quantifying the total lead time (TLT) of batch production as a probability distribution and sensitivity analysis reveals the ranking of sub-processes by impact on TLT. Based on these results, what-if analyses are performed to evaluate effects of investments, resource allocations and process improvements on TLT. An industrial case study was performed at a production site for Parenterals of F. Hoffmann-La Roche in Kaiseraugst, Switzerland, where the presented method supported analysis and decision-making of production enhancements.
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1. Introduction

Reliable supply of medicinal products is one of the most critical missions of the pharmaceutical industry. Short as well as stable lead time in production is demanded for all agents in the industry as a consequence of that. However, pharmaceutical manufacturing is not simple straight-forward production, but processes are regulated by the standards of good manufacturing practice (GMP) and processes may run in parallel to each other. For example in sterile drug product manufacturing, i.e., production of injectables, steps such as visual inspection of filled products, batch record review and quality control activities are performed concurrently. Furthermore, a plant typically produces multiple products at different scales and with varying urgency, resulting from different stages of product lifecycle, i.e., from new to matured. These characteristics of the pharmaceutical industry make it difficult to estimate the total lead time, or the time between start and end of the production including all associated activities. Difficulties in establishing the overall picture about total lead time prevent management from identifying improvement potentials and obstruct reasonable allocation of process enhancements.

The total lead time is known to vary in many pharmaceutical facilities; hindering companies from having projectable deliveries which in turn are a prerequisite for reasonable safety stocks (Pool et al., 2011; Tallon, 1993). As a consequence of that, tools supporting the decision-making about scheduling, batch-sequencing and -sizing have been of paramount interest to researchers in Process Systems Engineering traditionally which resulted in a list of approaches tailored to specific challenges. An early case study at Eli Lilly (Blocher et al., 1999) on tablet manufacturing investigates effects of total lead time variability on the output of a pharmaceutical plant. By consulting top level information only, throughput time was reduced by one third (Blocher et al., 1999); which is an impressive example for the potential of process improvements in drug product manufacturing. More recently, Susarla and Karimi (2011) presented a simple mathematical approach to integrate campaign planning and resource allocation in multiproduct batch plants. Their tool PlanPerfect was released (Susarla and Karimi, 2012) to deal with scheduling problems such as batch sequencing in real-life situations; case studies (Susarla and Karimi, 2012) explore the potential of their methodology. Other researchers investigated the characteristics of production planning for clinical trials (Chen et al., 2012, 2013) or market introductions of pharmaceutical products, considering challenges such as requested

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Nomenclature

Abbreviations

AIM	automated inspection machine
BRR	batch record review
BRC	batch record closure
CIP	cleaning in place
CPM	Critical Path Method
EWO	Enterprise-Wide Optimization
FDA	Food and Drug Administration
GMP	good manufacturing practice
MCS	Monte Carlo simulation
MES	Manufacturing Execution System
PKau	Parenterals Kaiseraugst, a Roche facility for sterile drug product manufacturing
QA	quality assurance
QC	quality control
R&D	research and development
RFID	radio frequency identification
SIP	sterilization in place

Indices

α	number of batches
i, j	sub-processes
n	number of sub-processes

Parameters and variables

$R(i,j)$	Spearman rank order correlation coefficient between sub-processes i and j
X_i	time stamp for sub-process i
LT	lead time of a sub-process
TLT	total lead time of production processes

label change and forecasting inaccuracy (Hansen et al., 2011). Moniz et al. (2012) focus on the challenge of combining regular and non-regular production in their work where solving the scheduling problem is supported by the Resource-Task Network. Stefansson et al. (2011) elaborate the qualities of continuous and discrete time models for solving large scheduling problems in the pharmaceutical industry and conclude that continuous time formulations can solve larger problems and are more accurate. Shah and Ierapetritou (2012) define a multisite multiproduct planning and scheduling approach as an extension of a singlesite method (Li and Ierapetritou, 2010). Pacciarelli and D'Ariano (2012) address the problem of data reliability in their work and perform a case study in drug product manufacturing with implementing radio frequency identification (RFID) technology. They conclude that the effect of enhanced data quality on the accuracy of production schedules is significant and can increase productivity dramatically (Pacciarelli and D'Ariano, 2012). Grossmann (2012) summarizes the current state of Enterprise-Wide Optimization (EWO) and emphasizes the importance of establishing wholistic approaches to deal with entire supply chains.

Latest efforts on lead time optimization with a focus on pharmaceutical production include the work of Brown and Vondrácek (2013) which applies time-based manufacturing methodologies to two Dutch pharmaceutical companies and investigates the relation between throughput time and delivery dependability. Kabra et al. (2013) apply State-Task Network based mixed integer programming for multi-stage production processes, considering constraints such as shelf-life limitations or late delivery penalties. Fumero et al. (2013) propose combining strategic, tactical and operational decision making into one integrated framework to balance trade-offs from multiple management levels best when designing a supply chain as a whole. Corsano et al. (2014) expand this concept of integrating strategic, tactical and operational level and evaluate three solution strategies when designing batch plants and strategic supply chain simultaneously. Chu et al. (2014) propose the combination of mixed integer programming and agent-based modelling to solve scheduling challenges in large-scale batch productions and perform successful case studies at a chemical company.

Most of these methods dealing with optimization of pharmaceutical production are not considering batch-to-batch variability of lead time satisfactorily. In the pharmaceutical production, this variability can be a decisive factor because of the incorporation of new products to existing production schedules or dynamic rescheduling on a regular basis due to priority changes. Actually, data recordings in pharmaceutical processes are excellent because GMP requests production to be well documented, which is done increasingly in electronic form. Thus, this situation calls for scientific contributions to exploit this potential of dramatically increased data availability. In addition, there have been no case studies reported on Parenterals/sterile drug product manufacturing, a key technology for biological medicines which are increasing the market share of the pharmaceutical industry.

In this work, we present a data-based method to assess and improve the total lead time of pharmaceutical production and then predicting future total lead time based on a probabilistic approach, employing Monte Carlo simulation (MCS). The method consists of five phases: (1) set up lead time model, (2) fit probability distributions, (3) perform MCS and sensitivity analysis, (4) perform what-if analysis and (5) derive managerial implications. This work defines the total lead time (*TLT*) as the time between start of production and release of products to the next process. By completing the first three phases, a probability distribution of the *TLT* is obtained by MCS as a summation of the probability distributions that represent the individual lead times (*LT*s) of the sub-processes. Improvement opportunities are then identified by analyzing the sub-processes sensitive to the *TLT* distribution; finally, futuristic situations are simulated by What-if analysis, and managerial implications can be obtained.

The method was applied as a case study to the new Parenterals manufacturing facility of Roche in Switzerland already during the facility start-up. The facility comprises of a compounding and three filling units, each dedicated to one kind of dosage form; namely liquid vials, lyophilized vials and pre-filled syringes. Using data from a sample of 24 test batches, a model was created to quantify the distribution of the *TLT*, and possibilities for improving *TLT* distributions were found by sensitivity analysis. The concluding What-if analyses supported deriving various managerial implications, which were useful for further start-up activities of the facility. This paper is organized as follows. In Section 2 the methodology is introduced and then applied to a real life case study in Section 3 followed by Section 4 which contains conclusions and outlook.

2. Methodology

Fig. 1 shows an overview of the proposed method, consisting of five phases. The first phase, *Setup Lead Time Model*, derives a single chain of relevant sub-processes, and defines the equation of *TLT* as the sum of the durations of these consecutive sub-processes. In the second phase, a probability distribution that represents the scattering of obtained data is determined for each sub-process, in the algorithm referred to as *Fit Probability Distribution*. Then, in the third phase, *Perform Monte Carlo Simulation and Sensitivity Analysis*, the *TLT* is calculated and the impact of sub-processes on *TLT* is quantified. In the fourth phase, *Perform What-if Analysis*, hypothetical enhancements are assessed by including scenarios for these sub-processes and re-running the MCS. Lastly, in the fifth phase,

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