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Simulation-optimization approach to clinical trial supply chain management with demand scenario forecast

Ye Chen, Linas Mockus, Seza Orcun, Gintaras V. Reklaitis*

Purdue University, West Lafayette, IN 47907, USA

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ABSTRACT

In the pharmaceutical industry, the development activities that are required to bring a new drug to market involve considerable expense (upwards of $1 Billion) and can take in excess of 10 years. Clinical trials constitute a critically important and very expensive part of this development process as the associated supply chain encompasses producing, distributing and administering the candidate therapy to volunteer patients located in different geographic regions. A number of different approaches are being pursued to reduce clinical trial costs, including innovations in trial organization and patient pool selection. In this work, we focus our attention on improved management of the clinical supply chain. A simulation-optimization approach is presented, including patient demand simulation and demand scenario forecast, mathematical programming based planning, and discrete event simulation of the entire supply chain. Three case studies with different demand types are reported and compared to demonstrate the utility of the proposed approach.

1. Introduction

New drug development follows an extended sequence of steps, including discovery, animal trials, FDA application, product and process development, three phases of clinical trials, FDA filing and approval, and launch. As a result it takes many years and considerable expense (upwards of $1 Billion) to bring a new drug to market. The discovery phase aside, clinical trials constitute a very expensive part of the development process. Normally, clinical trials with different test objectives (e.g. safety, efficacy, side effects) are conducted at the same time to expedite the new drug development process, thus further complicating clinical trial supply chain management. It has become more and more critical to have an optimized clinical trials supply chain management process to accelerate the new drug development process and reduce the total cost for a pharmaceutical company.

A substantial amount of work has been reported in the process industry supply chain management and optimization area, but only a limited literature has addressed the issues faced in the pharmaceutical industry. Shah (2004) provided an overview of the state of pharmaceutical industry related research and analyzed the key issues and strategies for pharmaceutical supply chain optimization. From Shah's review paper, there are research activities in discovery pipeline and development management, process development and plant design, as well as production planning and scheduling, but few references can be found in the clinical supply chain management area. There does exist literature that addresses issues such as the design of clinical trials, patient pool selection, and the drug delivery process. For example, Monkhouse, Carney, and Clark (2006) discussed the design and development of clinical trials in some detail and provided the basic knowledge necessary to conduct pharmaceutical clinical trials. Byron (2002a, 2002b) introduced the interactive voice response (IVR) systems, which are commonly used to manage clinical trial drug delivery process. Dowlman et al. (2004) proposed the use of a simulation model of an IVR-managed supply system to evaluate the outcomes and select the best strategy among a pre-defined supply strategy pool including a variety of supply strategies and scenarios. However, the management of an entire clinical trial supply chain and approaches to reducing its operational cost have not been addressed in the above references and has limited attention to date. Abdelkafi, Beck, David, Druck, and Horoho (2009)'s work is closely related with our work. In that work an approach to selecting the best supply plan was reported which attempted to balance the costs and the risk of short supply, and the Bayesian principle was utilized to reevaluate supply strategies over time. However, Abdelkafi's work only focuses on the drug supply part without considering the manufacturing part, which is also important in a clinical trial supply chain management problem.

Traditionally, the pharmaceutical industry uses batch processes to manufacture pharmaceutical products both at the pilot and the commercial scale. Since these batch facilities are usually shared across various products, especially for the quantities needed for

* Corresponding author.
E-mail address: reklaiti@purdue.edu (G.V. Reklaitis).

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Nomenclature

Indexes

i	material
j	process
k	campaign order
q	plant
t	time
x	expiration time
r	demand scenario

Sets

JO_i	processes which produce material i
JI_i	processes which consume material i
J_q	processes which could be conducted in production plant q

Parameters

P_{ir}	probability that demand scenario r occurs for material i
C_i^h	holding cost per unit and time for material i
C_i^w	cost of disposing one unit of material i
F_j	fixed cost of running a campaign for process j
C_j^m	variable cost of producing one unit of material by running process j
C_i^p	penalty cost for missed demand for per unit material i
b_j	batch size of production process j
τ_j^v	batch processing time by running process j
τ_j^f	set-up time of a campaign by running process j
MC_q	maximum number of concurrent campaigns could happen in production plant q
β_{ij}	proportion of output of material i from production process j
CD_{itr}	cumulative demand for material i by time t for scenario r
$S_i^{\min}$	minimum inventory requirement of material i
Sl_i	shelf life of material i
H	planning horizon
$B_j^{\min}, B_j^{\max}$	minimum/maximum number of batches in one production campaign for process j
$N_q^{\min}, N_q^{\max}$	minimum/maximum number of campaigns in production plant q
$BS_j^{\min}, BS_j^{\max}$	minimal/maximal batch size for distribution campaign

Continuous variables

p_{ikqt}	amount of material i produced by production campaign k in plant q by time t
ts_{kq}	start time of production campaign k in plant q
T_{kq}	duration of production campaign k in plant q
B_{jtx}	batch size of distribution process j started at t by shipping material will expire at time x
B_{jt}	batch size of distribution process j started at t
M_{it}	amount of material i that becomes available at time t
CM_{it}	cumulative amount of material i available by time t
W_{itr}	amount of material i that is wasted at time t because of shelf life
CW_{itr}	cumulative amount of material i that is wasted up to time t for scenario r
D_{itxr}	demand for material i with expiration x at time t for scenario r
S_{itxr}	inventory of material i with expiration x at time t for scenario r
SD_{itxr}	satisfied demand for material i with expiration x at time t for scenario r
SCD_{itr}	cumulative amount of material i that is satisfied up to time t for scenario r
SL_{itr}	slake variable of cumulative amount of material i that is missed by time t for scenario r

Binary variables

$\lambda_{kq} = 1$	if campaign k in production plant q is actually processing
$v_{kqj} = 1$	if process j is assigned to campaign k in production plant q
$f_{kqt} = 1$	if campaign k in production plant q finishes by time t
$O_{itr} = 0, i \in I^F$	if material i is wasted at time t under scenario r
$Z_{jt} = 1$	if one batch is started at time t for distribution process j

Integer variables

y_{kqj}	number of batches of campaign k in production plant q by running process j

clinical trials, it is necessary to decide the order, amount and timing of the products to be produced on these shared resources. These decisions can have a large economic impact on the company at the clinical trials stage, because missing the delivery of trial dosage to patients can significantly delay completion of the trial and hence delay the time to market which in turn can mean significant loss of revenue. Therefore, the key technical challenges in managing a clinical trial supply chain are to meet the needs of the clinical sites, so that patients are fully supplied once they are enrolled while minimizing total operating cost. Deterministic mixed integer linear programs (MILP) optimization methods have been proposed to solve resource constrained project planning and scheduling problems (see Floudas & Lin, 2004, which presented a comprehensive review of these approaches). Most of the work reported is confined to a deterministic context; however, for a clinical trial supply chain, not only patient enrollment is highly variable, but uncertainties also arise in manufacturing and shipment lead times, in process failures and in production yields. Jain and Grossman (1999) addressed the problem of a single project with no resource constraints and task success uncertainty. Honkomp (1998) dealt with the problem of both project selection and project scheduling with task success uncertainty. Most of these and related references take into account stochastic elements by incorporating expected value of uncertainties into planning models to generate period plans that buffer the effect of uncertainties. However, the horizon of a clinical trial materials supply chain (~1–2 years), is significantly shorter than that of a commercial supply chain, (~10+ years). Therefore, the strategies utilized to buffer the uncertainties in commercial supply chains become ineffective as expected values cannot be effectively used as targets. Moreover, a typical clinical trial is terminated after 1–2 years and thus the drugs leftover at the end of clinical trial must be treated as wastage since unused materials cannot be reused and must be disposed. By contrast in traditional supply chain planning horizon lasts for more than 10 years and the leftover inventory at the end of the horizon are not considered to be a significant cost. Instead the focus is on average inventory cost. In the pharmaceutical industry, the cost of unused clinical trial dosage can be quite large and thus there is significant benefit in reducing this cost