Computers and Chemical Engineering 42 (2012) 168–177

Contents lists available at SciVerse ScienceDirect

Computers and Chemical Engineering

journal homepage: www.elsevier.com/locate/compchemeng

# Integrated supply chain planning for multinational pharmaceutical enterprises

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ARTICLE INFO

*Article history:*
Received 28 September 2011
Received in revised form 28 February 2012
Accepted 8 March 2012
Available online 22 March 2012

*Keywords:*
Integrated planning
Pharmaceutical supply chains
Multinational enterprises
Production planning
Procurement
Distribution
Transfer prices

ABSTRACT

The management of global supply chains is highly complex and vital for multinational pharmaceutical enterprises. Global integrated planning in multi-site, multi-echelon network of a multinational company has attracted some academic interest. However, the focus has largely been on efficient solution strategies for large problems. In this work, we develop simple yet powerful MILP model for multi-period enterprise-wide planning. We represent the entire enterprise in a seamless fashion with a granularity of individual task campaigns on each production line. Our model integrates procurement, production, and distribution along with the effects of international tax differentials, inventory holding costs, material shelf-lives, waste treatment / disposal, and other real-life factors on the after-tax profit of the company. To demonstrate the performance of our model, we solve two example problems of planning multinational pharmaceutical enterprise. For our evaluation, we consider an industrial scale planning problem for a supply chain network consisting of 34 different entities and producing 9 different products, for a period of 5 years.



## 1. Introduction

The global pharmaceutical industry is grappling with tremendous turmoil in the marketplace and a dramatically changing competitive landscape. This is mainly due to the numerous mergers among different companies and the upsurge in generic manufacturers. Fierce market competition, peaking patent cliffs, mounting R&D costs, shrinking product pipelines, and stringent regulatory protocols are bringing a paradigm shift in the way pharmaceutical enterprises operate. Companies are beginning to realize that past practices will not meet future market needs. The past decade reflects a significant imbalance between new product introductions and patent losses (Pharmaceutical industry outlook – Zacks Equity Research, March 2011). This is expected to continue for the next few years. Also, the new products are not expected to generate the same levels of sales as the products losing patent protection. With revenue growth stalling or slowing down, companies are resorting to cost-cutting to drive bottom-line growth. Although pharmaceutical companies are not known to be the best practitioners of the supply chain models, optimization of supply chain operations is known to improve the bottom lines in several other industries such as airline, refining, semiconductor, etc. This has also prompted the pharmaceutical companies to begin focusing on exploiting economies of scale in manufacturing and improving the management of resources such as facilities, equipment, materials, human, information, and finances.

Fig. 1 shows a schematic of a typical large multinational pharmaceutical enterprise. It involves functions such as raw material sourcing, primary or API (active pharmaceutical ingredient) manufacturing, secondary manufacturing, warehousing, distribution, etc. Such a configuration requires frequent transfers of materials (raw, intermediates, products, packaging, etc.) among the different sites across the globe. These material transfers not only involve time and normal operational costs, but also a slate of administrative and regulatory procedures and costs. Such costs include import duties and corporate taxes to be paid to the local governing authorities, transfer prices for material flows among the company's various sites, etc. Since the taxes and duties vary from one country to another, they can be intelligently exploited to maximize after-tax profits. Another key characteristic of a typical pharmaceutical enterprise is its high-valued material inventories. This is to ensure a high level of customer satisfaction in the face of any operational disruptions and capitalize on any unexpected opportunities (e.g. increase in demand during a disease outbreak or natural calamity). However, costly inventories freeze capital, and are undesirable for many reasons. Clearly, the pharmaceutical operations involve trade-offs, and require intelligent decision making, making operational planning and decision making a complex and crucial task.

Now, the decisions made at the enterprise-level affect significantly the operations at individual entities (API manufacturing plants, secondary manufacturing plants, distribution houses, etc.). The entities perform many complex physicochemical

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doi:10.1016/j.compchemeng.2012.03.002

**Nomenclature**

*Indices*

| | |
|---|---|
| $i$ | task |
| $l$ | production lines |
| $m$ | materials |
| $s$ | site |
| $t$ | time interval |
| $p$ | period |

*Superscripts*

| | |
|---|---|
| $L$ | lower limit |
| $U$ | upper limit |

*Sets*

| | |
|---|---|
| $L_s$ | lines that are at site $s$ |
| $I_l$ | tasks that line $l$ can perform |
| $M_s$ | materials that site $s$ either consumes or produces |
| $IM_s$ | materials that site $s$ consume |
| $OM_s$ | materials that site $s$ produce |
| $PC_m$ | set of all precursor materials for final product $m$ |
| $T_p$ | intervals in period $p$ |
| FP | set of final products for E |
| $PC_m$ | set of all precursor materials of a final product $m$ in E |

*Parameters*

| | |
|---|---|
| $\sigma_{mi}$ | mass ratio for material $m$ in task $i$ |
| $\delta_{mss'}$ | lead time for procuring material $m$ at $s'$ from $s$ |
| $A_m$ | shelf-life of material $m$ |
| $h$ | length of an interval $t$ |
| $\tau^U_{ils}$ | cycle time of $i$ in $l$ at $s$ for minimum resource allocation |
| $\tau^L_{ils}$ | cycle time of $i$ in $l$ at $s$ for maximum resource allocation |
| $Q^U_{ms}$ | storage capacity of material $m$ at site $s$ |
| $B_{ils}$ | batch size of task $i$ on line $l$ at site $s$ |
| $D_{mst}$ | demand of material $m$ at site $s$ at time $t$ |
| $OSQ_{mt}$ | overall safety stock limit for product $m$ and its precursor material at time $t$ |
| $SQ_{mst}$ | safety stock of material $m$ at site $s$ at time $t$ |
| $TP^U_{mss'p}$ | lower limit on transfer price for $m$ from $s$ to $s'$ during period $p$ |
| $TP^L_{mss'p}$ | upper limit on transfer price for $m$ from $s$ to $s'$ during period $p$ |
| $a_{ils}$ | constant for processing cost |
| $b_{ils}$ | constant for processing cost |
| $hc_{msp}$ | cost of holding unit material $m$ at site $s$ during period $p$ |
| $\gamma_{msp}$ | penalty for violating safety stock of $m$ by unit amount at $s$ during $p$ |
| $d_{mss'p}$ | duty for importing unit quantity of $m$ from $s$ to $s'$ during $p$ |
| $tax_{sp}$ | corporate tax at site $s$ during period $p$ |
| $Dep_{sp}$ | depreciation rate at site $s$ for a period $p$ |

*Variables*

| | |
|---|---|
| $n_{ilst}$ | number of batches of task $i$ in line $l$ at site $s$ during $t$ |
| $cl_{ilst}$ | length of a campaign of task $i$ in $l$ at $s$ during $t$ |
| $Q_{mst}$ | net usable stock of material $m$ at site $s$ at time $t$ |
| $OQ_{mss't}$ | amount of material $m$ received from site $s$ to site $s'$ at time $t$ |
| $Q^a_{mst}$ | net stock of material $m$ with an age of $a$ intervals at site $s$ at time $t$ |
| $OQ^a_{mss't}$ | amount of $m$ with an age of $a$ intervals received at $s'$ from $s$ at time $t$ |
| $q^a_{mst}$ | amount of $m$ with an age of $a$ intervals consumed at $s$ during interval $t$ |
| $\Delta OSQ_{mss't}$ | amount of material $m$ at time $t$ violating overall safety stock limits |
| $\Delta SQ_{mst}$ | amount of $m$ at $s$ violating site-specific safety stock limits at time $t$ |
| $\Delta TP_{mss'p}$ | differential transfer price over and above the minimum |
| $PU_{lsp}$ | total idle time of line $l$ at site $s$ during period $p$ |
| $R_{sp}$ | revenue of site $s$ during period $p$ |
| $IBT_{sp}$ | taxable income of site $s$ during period $p$ |
| $ATP_{sp}$ | after tax profit of site $s$ during period $p$ |
| $NP$ | total profit of E |

transformations and value-addition steps before the drugs reach the consumer. The API plants transform raw materials into active ingredients. The secondary manufacturing plants add varieties of excipients to these active ingredients to produce drugs in their consumable forms (e.g. tablets, solutions, pastes, gels, inhalers, etc.). The distribution houses use these drugs in bulk quantities and package them in suitable sizes with appropriate labels (e.g. bottles, tablet strips and syringes) that are specifically appropriate for each market.

Most tasks described above involve multi-step batch operations that require limited and shared resources such as equipment, human, utilities, etc. A typical manufacturing (API or secondary) or packaging plant may employ several production lines to perform these operations. Fig. 2 shows the configuration of a typical pharmaceutical plant with production lines and multi-step operations. Most plants are multipurpose batch plants that produce multiple active ingredients or products. Optimal allocation of adequate resources and sequencing of operations on production lines require involve a huge number of possible combinations, which easily becomes computationally intractable as the numbers of products and/or plants increase. In addition, pharmaceutical manufacturing is strictly and highly regulated, and operations on the same line may involve long and expensive cleaning between successive steps. Thus, holistic and integrated decision making at the enterprise level considering the nuances of individual entities and functions and their complex interactions is extremely difficult and critical for the economic sustainability of a pharmaceutical company.

Global integrated enterprise-wide planning has attracted some interest from the academic community with some work on pharmaceutical industry. McDonald and Reklaitis (2004) highlighted the importance of considering financial aspects such as taxes, duties and transfer pricing in supply chain optimization models. Grossmann (2004, 2005) and Varma, Reklaitis, Blau, and Pekny (2007) reviewed in detail the current research trends in enterprise-wide optimization and highlighted current challenges and future research opportunities.emerging future challenges. They stressed the need for developing novel computational models and algorithms to solve real-world problems and strengthen the economic performance and competitiveness of the process industries. Shah (2005), Barbosa-Póvoa (2009), and Papageorgiou (2009) reviewed existing models and key issues in pharmaceutical supply chains.

Cohen and Lee (1988) presented an enterprise-wide optimization model for a company operating in batch mode, and determined costs for multiple operational scenarios. Timpe and Kallrath (2000) developed a MILP model for optimizing a multi-site network with production, distribution, and marketing constraints. However, the model was difficult to solve for large problems. Thus, a need exists