Bi-Objective Optimization for the Clinical Trial Supply Chain Management

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Abstract
In the pharmaceutical industry, clinical trials constitute a critically important and very expensive part of the new drug development process. A clinical trial supply chain will terminate after 1-2 years, and leftovers at the end of clinical trials constitute an important financial cost since all the unused materials should be disposed after clinical trial completion. Normally, extra safety stocks are kept in the supply chain system to increase the customer service level (CSL), however more leftovers are introduced by increasing safety stocks. By considering a bi-objective optimization using a weighted-sum approach, we build an approximation to the CSL vs. leftovers Pareto frontier. This will support the evaluation of the trade-off between these two performance metrics and thus the selection of a safety stock level that optimally balance CSL and leftovers. The entire framework includes four modules: demand forecasting, an integrated planning and optimization formulation, a discrete event simulation model and an outer loop optimization process. An industrially motivated case study is presented to demonstrate the utility of this proposed approach.

Keywords: Clinical Trial, Supply Chain, Safety Stock, Bi-Objective Optimization

1. Introduction
Clinical trials constitute a critically important and very expensive part of the new drug development process due to their high failure rate and extended duration. It has become more and more critical to have an optimized clinical trials management process to accelerate the new drug development process and reduce the total cost for a pharmaceutical company. A number of different approaches are being pursued to reduce clinical trial costs, including innovations in trial organization, randomization methodology selection, and supply strategy selection, as described in Peterson et al. (2004)’s work. However, these approaches do not constitute an actual optimization strategy since their outcomes are not used to modify the prior strategies. Abdelkafi et al (2009)’s work is the start point of applying optimization technique in the clinical trial supply chain management area: it tries to select the best supply plan by attempting to balance the costs and the risk of short supply. However, it only focuses on the drug supply part of clinical trial without considering the production part.

The entire clinical trial supply chain management problem is composed of a set of inter-related planning and scheduling decisions which seek to better synchronize all activities, transactions, operations and organizations involved in the clinical process. The key challenges of this problem are to fully satisfy the needs of clinical sites, avoid oversupply and reduce leftovers. Normally, safety stock is kept in the supply chain system as a hedge against the stochastic demands and thus to increase CSL. For a clinical trial supply chain, leftover product remaining on hand at the end of the trial, constitute an important financial cost which increases with higher safety stocks.
Leftovers must be considered as wastage since such drug products cannot be reshipped to other clinical sites or reused, according to FDA regulations. Chen et al. (2010) proposed a simulation-base optimization approach to deal with clinical trial supply chain management and this paper presents an extension of that work. Specifically, based on the simulation-optimization computational framework, a bi-objective based weighted-sum approach (Freitas, 2004) is used to build an approximation for the CSL vs safety stock Pareto-frontier. This will allow the pharmaceutical company to select the safety stock levels which optimally balance the CSL and leftovers performance.

2. Proposed Approach

2.1. Simulation-Optimization Computational Framework

The computational framework proposed for this work consists of stochastic demand forecasting, deterministic planning and optimization, a discrete event simulation of the entire supply chain, and an outer loop searching process to optimize the safety stock levels based on bi-objective: CSL and leftovers, as depicted in Figure 1.

Figure 1 Simulation-optimization computational framework

Stochastic demand forecasting occurs via a simulation model which represents the patient enrolment process at the clinical sites and serves to determine the number of drug package needed at the clinical sites. The forecasted demand scenarios can be generated based on these demand values. Given demand scenarios and preset safety stock levels, the planning and optimization part is executed to determine the manufacturing and shipping plans. This is accomplished by solving an MILP formulation using GAMS 23.2-CPLEX 12.1. The resulting plans serve as the driver for the simulation model of the entire supply chain, which is built in the discrete event simulation software ExtendSim 7, and which captures all activities, operations and processes involved in this clinical trial. The planning and simulation parts are executed in the rolling horizon mode for each timeline and include sampling from the distributions of the uncertainty parameters of the system. To capture the uncertainties and effectively assess the performance of the entire supply chain, here represented by the CSL and leftovers, multiple optimization-simulation timelines are implemented by repeatedly sampling the uncertain parameters in the classical Monte Carlo mode. Based on a series of replications, an outer loop search algorithm is used to optimize the bi-objective performance function by iterating on the safety stock levels until convergence is achieved.

2.2. Planning and Optimization

Traditionally, multi-purpose batch plants are widely used in the pharmaceutical industry. Since these batch facilities are usually shared across various products, it is necessary to decide the order, amount and timing of the products to be produced on
these shared production resources. A discrete time MILP formulation method (Papageorgaki & Reklaitis, 1990) is used to formulate the planning model, in which both production and distribution processes are treated as one task \( i \), conducted on equipment \( j \). Each task operates in batch campaign mode. A distribution campaign is represented as a single batch without setup time but with a variable batch size. Since the batch processing time is a characteristic of the equipment used, its value is treated as a given parameter.

### 2.2.1 Objective

The objective of this model is to minimize the total operation cost, including the fixed setup cost associated with starting a campaign, variable processing cost, holding cost, wastage cost for expired products and leftovers, penalty cost for unsatisfied safety stock levels, and penalty cost for missed demand in clinical sites.

\[
\text{Min} \quad \text{TotalCost} = \sum_{i \in I} \sum_{j \in J} \sum_{f \in F} C_{cf} \left( \sum_{s \in S} X_{isy} \right) + \sum_{i \in I} \sum_{j \in J} \sum_{f \in F} C_{df} \left( \sum_{s \in S} X_{df} \right)
\]

**Setup cost**

\[
+ \sum_{i \in I} \sum_{j \in J} \sum_{f \in F} P_{cf} \left( \sum_{s \in S} P_{sif} \right) + \sum_{i \in I} \sum_{j \in J} \sum_{f \in F} C_{df} \left( \sum_{s \in S} P_{sif} \right)
\]

**Variable cost**

\[
\sum_{s \in S} C_{ds} \left( \sum_{i \in I} S_{is} \right) + \sum_{s \in S} C_{fe} \left( \sum_{f \in F} E_{sif} + S_{sif} \right) + \sum_{s \in S} \sum_{f \in F} C_{penalty} (D_{sif} - SD_{sif}) + C_{penalty} (SS_{f} - S_{sif})
\]

**Inventory holding cost**

**Wastage and leftovers**

**Penalty costs**

### 2.2.2 Constraints

Several constraints are included in this MILP planning model to describe the entire supply chain structure. The model comprises different set of constraints related to the campaign-batch mode, mass balances, satisfied demand, shelf life/expired material constraints, and inventory capacity. The entire MILP model is solved to generate the production campaign and distribution plans, which serve as the driver for the simulation model which in turn is executed to evaluate the performance of entire supply chain.

### 2.3. Bi-objective Optimization in the Outer Loop

One advantage of this proposed simulation-optimization framework is that it can determine the optimal amount of safety stock levels with respect to the bi-objective performance function using an outer loop direct search optimization method. The objective function for this problem can be mathematically described in Eq. (1).

\[
\text{MIN} \quad J(SS) = \sum_{s} \left[ \omega_1 \Delta CSL_s + \omega_2 LTR_s \right]
\]

\[
CSL_s = \frac{\sum_{f \in F, t \in T} \text{satisfied demand}_s (f, t)}{\text{Total Demand}_s}
\]

\[
CSL_s + \Delta CSL_s = CSL_{s}^{tar}
\]

\[
LTR_s = \frac{\text{Leftover}_s}{\text{Total Demand}_s}
\]

Here \( CSL_s \) is the estimated CSL of material \( s \) from current simulation, \( CSL_{s}^{tar} \) is the target CSL of material \( s \), and \( \Delta CSL_s \) is the deviation of current CSL from the target CSL. \( LTR_s \) is the normalized leftover ratio, leftover of material \( s \) divided by its total demand. \( \omega_1 \) and \( \omega_2 \) are the weights for the two objectives. The combined objective is to minimize the weighted sum of the deviations of target CSL’s and leftover ratios.
With preset $\omega_1$ and $\omega_2$ value and safety stock setting, the planning and simulation parts work together to evaluate the performances for the entire supply chain: CSL and leftover ratio (LTR), which are used to update the current safety stock level setting, shown in Eq. (2). The entire searching process is driven by the weighted sum of the deviations of target CSL and normalized LTR until the final optimization objective $(|J(SS)^n - J(SS)^{n-1}| < \varepsilon_1)$ or safety stock level $(|SS^n - SS^{n-1}| < \Theta_2)$ converges. The final obtained safety stock levels are optimal for that set of weighting factors,

$$ss_s^{n+1} = ss_s^n + \alpha^n_s (\omega_1 \Delta CSL_s^n - \omega_2 LTR_s^n)$$

where $\alpha^n_s = \frac{ss_s^n - ss_s^{n-1}}{J(SS)^n - J(SS)^{n-1}}$ (2)

The safety stock levels obtained for different $\omega_1$ and $\omega_2$ parameter values, serve to define an approximation for the CSL vs. LTR Pareto frontier. The frontier serves to support corporate strategic decisions regarding the appropriate balance between financial cost and customer service level.

3. Case Study and Results

The utility of the proposed simulation-optimization approach and its bi-objective optimization process is demonstrated by means of a case study. The case problem is drawn from Chen et al. (2010): the associated clinical trial supply chain network is shown in Figure 2. Safety stocks are kept in the US distribution center and European intermediate distribution center and optimized in the outer loop. Three case studies with different $\omega_1$ and $\omega_2$ values are investigated to obtain the final converged safety stock and used to construct the CSL vs LTR Pareto frontier.

Figure 3 shows the outer loop optimization process for the safety stocks in the EU distribution center and the optimization objective, in which $\omega_1=1$ and $\omega_2=0$. We can note that after 8 iterations, the optimization objective starts to converge and the search process is terminated after 18 iterations. For different $\omega_1$ and $\omega_2$ setting, different converged safety stock levels are obtained with corresponding CSL and LTR values. Figure 4 shows three points obtained from case studies for EU Drug 1: point A is obtained with $\omega_1=0$ and $\omega_2=1$, and the associated converged safety stock is 0 packages; point B is obtained with $\omega_1=0.8$ and $\omega_2=0.2$, and the associated converged safety stock is 170 packages; point C is obtained with $\omega_1=1$ and $\omega_2=0$, and safety stock is 913 packages. The set of such solution points can be used to construct the CSL vs LTR Pareto frontier, which allows the pharmaceutical company to choose an appropriate safety stock value on the basis of other strategic considerations.

4. Conclusion

The proposed multi-level simulation-based optimization approach effectively allows treatment of the clinical trials supply chain planning problem. However, the approach is quite computationally intensive since each iteration requires around 30-50 replications to converge and around 10 hours to finish. This is because each cycle through the outer optimization loop, requires evaluation of the stochastic bi-objective function which in turn requires significant numbers of replicates of the Monte Carlo simulation and imbedded planning problem solution. There are a number of ways to reduce the computational burden, such as through parallelization of the Monte Carlo timelines. Moreover, the use of this framework does allow access to more detailed level information about the conduct of the trails. For instance, the progression of each patient
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can be tracked during the course of the administration protocol. Consequently if a patient’s treatment is missed because there are not enough drugs on hand when the patient arrives at the clinical site to receive the drug package for the next week this occurrence can be recorded. Such an occurrence not only invalidates that patient as a contribution to the clinical trial but as a result the drug packages previously administered to this patient are wasted. This amount can be recorded and thus, the cost of undersupply can be quantified in terms of ineffectively used drug packages. While failure to supply the patient when needed also results in other costs, the reduction of under and oversupply to a single metric of wasted drug packages has attractive features. Additional beneficial studies based on the use of such tracked patient information can be obtained from the simulation model. For instance one could examine progressively increasing incentive strategies which would encourage patients to persist in the treatment protocol.

Figure 2 Clinical trial supply chain network

Figure 3 Outer loop optimization process

Figure 4 CSL vs LTR

References