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MULTI-ECHELON NETWORK OPTIMIZATION OF PHARMACEUTICAL COLD CHAINS: A SIMULATION STUDY

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ABSTRACT

To ensure quality of pharmaceutical raw materials and products it is very important to monitor specific factors throughout supply chain. In cold chains, temperature is closely controlled and monitored. Furthermore, it is critical to retain all associated information artifacts from a reporting, inspection and auditing standpoint. Loss in information can translate to significant monitory losses to parties involved. Consequently, cost not only includes all traditional supply chain costs, but also contains costs associated with penalties due to information loss/inaccuracy. Therefore, managing pharmaceutical cold chain costs is more challenging than managing traditional supply chain costs. This paper studies a typical cold chain and costs associated with a typical multi-echelon network under stochastic demand and probabilistic information handoff conditions. Dynamic equations are developed for individual nodes. A DOE is also proposed to understand sensitivity of key factors on costs. A simulation based optimization approach is adopted for the study.

1 INTRODUCTION

Cold chains are supply chains where temperature (and in many cases humidity) is controlled and monitored. Pharmaceutical components like Active Pharmaceutical Ingredients (APIs), biologics and vaccines, are all handled through cold chains. These chains are much more difficult to manage compared to the traditional supply chains due to several factors including, controlling temperature/humidity of materials (raw material, drug substance or drug products), continuous monitoring and accurate reporting, very less material shelf-life, stringent checks imposed by regulatory bodies, high probability of drug counterfeits, etc.

Different materials require different storage conditions, e.g. > 0^0C, but less than ambient (chilled), below freezing, or sometimes may even require temperatures < -160^0C (cryogenic) (Higgins et al. 2009). Extended periods of transit time increases risk to product quality by increasing probability of exposure to temperature excursions, humidity, light or atmosphere. Slight temperature excursions outside the pre-validated condition, for brief periods, may be acceptable provided stability data and scientific/technical justification prove that product quality is not affected (Health Product and Food Branch Inspectorate 2011). However, any significant deviations from this validated temperature range can significantly impact product quality. Thus, it is very important to control, monitor, report and document temperature attributes constantly throughout the chain. Inaccurate and untimely recording and reporting, or loss of information at the handoff points can result in significant penalties (monitory or legal) for the supply chain players. Zhang et al. (2008), state the importance of improved supply chain visibility which basically refers to better communication between different nodes involved with the supply chain. Information regarding demand data, sales, capacity levels, inventory, etc. is shared within the supply chains, including the cold chains (Schwarz and Zhao 2011). Along with the aforementioned information artifacts, we also study the probability of accurate and timely information exchange at the handoff points between echelons in the cold chain.

This paper describes the development of dynamic equations for a four-echelon network structure, with a potential to be expanded to multi-echelons. Additionally, a design of experiment is created and a simulation based optimization study is performed to understand the sensitivity of supply chain ownership, stochastic demands and probabilistic information transmission conditions on the overall cost for the pharmaceutical cold chains. This is a unique feature of our research as there are no studies that have used ownership cost and information transmission as factors to model supply chain under a simulation optimization environment for the pharmaceutical environment. Outcomes from this study are expected to provide important insights to the cold chain management issues and help companies make better decisions.

2 LITERATURE REVIEW

Life science supply chains, particularly the pharmaceutical supply chains and cold chains have not been researched adequately (Schwarz and Zhao 2011). Higgins et al. (2009) define a cold chain as a logistics environment, including storage, handling, and transportation, maintained within specified temperature ranges. It is very important to ensure that the pharmaceutical components, namely, drug products, drug substances and raw materials, stay within a pre-validated temperature range throughout the chain. Inappropriate storage and handling conditions can deteriorate product quality (Ames 2006). For example, oral vaccines lose their potency if they are not maintained between 2-8^{0}C during distribution, and if these vaccines are even accidentally exposed to freezing temperatures (Matthias et al. 2007).

Regulatory and standards-based organizations require detailed management of temperature-sensitive material during all steps of the supply chain (Bishara 2006a). Temperature / humidity data is required to be collected and documented over predetermined intervals. Furthermore, it is required that these recorded temperature data be readily available for review (Bishara 2006b). Loss of information during any phase in the cold chain can result in significant penalties. Subsequently, pharmaceutical cold chain costs are not only driven by the traditional supply chain attributes, such as inventory, demand, service level, etc., but are also influenced by additional material handling requirements and quality of information transmitted.

2.1 Monitoring Techniques and Technologies for Cold Chains

In order to monitor material temperature during transit and storage, it is a common practice to incorporate temperature sensing devices, place temporary or permanent data loggers inside the containers, or use Global Systems for Mobile Communications (GSMs), Time Temperature Indicators (TTI) and barcode readers. Based on data provided by these devices, the customer can make informed decisions whether to accept the shipment or not (Banker 2005). Additionally, information recorded (temperature readings) from such devices can be used to map time and location of the product in the supply chain and identify what point in the supply chain did the product encounter adverse conditions or any other problems.

Edwards (2007) discusses business opportunities for the RFID technology by comparing it with TTI labels, data loggers and chart recorders. Metzger et al. (2007), identify a major concern with implementing RFID technology. They express concern over continuous power supply to the RFID tags, as continuous power supply will ensure continuous temperature monitoring which in turn will improve the efficiency of the cold chain. Higgins et al. (2009) reiterate the need for real-time (or near real-time) tracking systems and digital integration, particularly for international movements.

Ames (2006) further points out another important outcome of continuous data monitoring and reporting. Since there is a high frequency of counterfeiting in pharmaceutical cold chains, constant monitoring can help improve product authentication process and prevent counterfeiting. The author further suggests unifying monitoring and anti-counterfeiting mechanisms into a comprehensive temperature-monitoring and documentation program.

2.2 Relevant Cold Chains Studies

Bishara (2006b) recommends mapping the entire process, associated environmental restrictions for products, and product flows through different stages. During the mapping phase, appropriate data elements should be identified. The need of data and the importance of data gathered will vary based on the role of an individual. Appropriate statistical and data analysis techniques can then be used in decision making.

Bogataj et al. (2005) study the effect of temperature perturbations on costs, annuity stream and NPV of the final product by employing an extended MRP model and described the system's state by set of first order linear differential-delay equations. Their study aimed to identify the appropriate controls which help maintain product quality through final delivery. O'Connor (2005) presents insight into the inconsistencies in the temperature during the transportation. It was noted that varying temperature at different sections inside the container significantly alter product quality. In this study it was found that the average temperature inside every pallet in the container was higher than the thermostat set. Failure to monitor and record these different sections inside the container will deteriorate product quality and make it difficult to understand the root cause of product failure.

As aforementioned, typically information sharing in supply chain dealt with sales data, demand data, inventory levels, etc. In recent years models have been developed around this information sharing. Schwarz and Zhao (2011) and compare the Fee-For-Service (FFS) with the Investment Buying (IB) strategy used in pharmaceutical supply chains based on information shared about demands and sales. However, none of the papers reviewed in literature associate cost with information inaccuracy or losses regarding the product attributes between different players of the cold chain.

3 MODEL DESCRIPTION

The schematic of a four-echelon (stage) system is shown in Figure 1. The system consists of five nodes, each node representing a firm or an organization in the pharmaceutical cold chain network. Raw material is procured from an external supplier by the manufacturer and processed to a final product (drug product or a vaccine) which is then shipped to the warehouse, flowing through the DCs to the retailer. The retailer is assumed to receive the final product partially from DC 1 and DC 2. An allocation problem exists when the product has to be shipped from warehouse to DC 1 or DC 2, allocation policy (described later) is used to determine proportion of supply to DC 1 and DC 2.

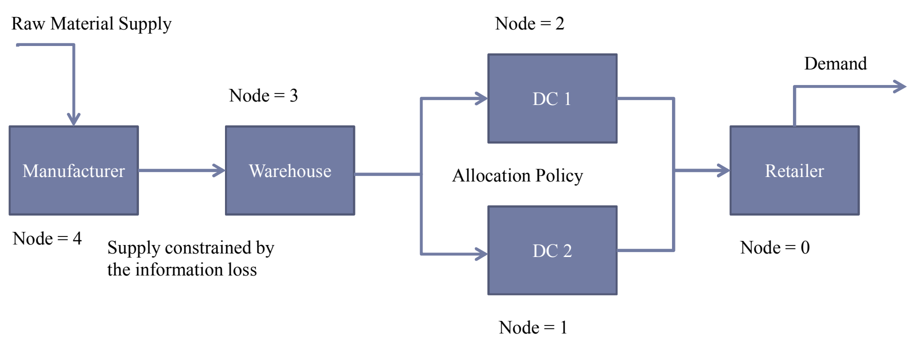

Figure 1: Four-echelon pharmaceutical supply chain.

Uncertainty is involved in both the demand and supply. The uncertainty in supply is a result of stochastic information loss assumed between the nodes. Loss of information beyond an acceptable level for the product will result in the entire shipment being discarded or quarantined for further lab tests and analysis. If the information is lost, or information is suspected to be distorted, it can be said that the product is compromised and there is a quality issue corresponding to the shipment received. This implies demand at the receiving node will not be satisfied due to supply shortages resulted from quality issues. Following notations are used:

ξ_n = Demand in period *n*;
l^i = Lead time of product to reach node *i*;
η_n^i = Quality check of product at node *i* in period *n*;
s^i = Base-stock level for *i*;
c^i = Cost per unit of product at node *i*;
c^P = Cost of information loss at hand-off between nodes;
α^i = Required type-I service level at node *i*;
Y_n^i = Outstanding orders of item *i* in period *n* that have not been delivered;
I_n^i = On-hand inventory level of item *i* in period *n* before the demand is realized = $\max\{0, NI_n^i\}$;
NI_n^i = Net Inventory for Product *i* in period *n*;
PC^H = Penalty cost incurred due to information loss at handoff;
P_n^i = Probability of information received at node *i* in period *n* ;
t^P = Threshold probability;
γ = All or Nothing function;
P_D = Proportion of Demand;
P_S = Proportion of Supply;
δ = Lost demand cost adjustment factor;
τ = Quarantine cost adjustment factor; and
γ_n^i = all-or-nothing function at node *i* in period *n*.

3.1 Four-echelon System Assumptions and Operations

A fixed lead time is associated between the two echelons, which corresponds to the ordering, transportation and manufacturing lead time. In this paper we only consider a single end-product for finite horizon (multiple periods). Based on the temperature and humidity conditions product characteristics are modeled with respect to the level of information loss. For instance some information loss is acceptable for non-controlled or ambient temperature conditions, but information regarding the controlled temperature (chilled, frozen, etc.) product is very critical hence we require negligible information losses. The end product demand is considered to be stochastic. The information related to the product, which includes the product characteristics and other information has to be logged either in a central server or at a server located locally at each node (organization) in the supply chain network. We assume there is a probability of information loss when the product is transferred from one node to another node.

An installation type periodic base-stock policy is used. Under this policy, at the start of each period if the inventory position (on-hand inventory + orders – backorders) falls below the base-stock level, order is placed to bring the inventory levels back to the base-stock level. Unsatisfied orders are backlogged. Type-I service level model is employed. In order to ensure system stability, we assume that that the average demand is less than the average supply, $E[\xi_n] \le E[\eta_n^i]$, at a node. At the beginning of each period the following sequence of activities occurs: i) the outstanding orders are updated, ii) on-hand inventory is updated, iii) demand is realized, iv) capacity is realized. The objective function for the four-echelon problem formulation is shown below:

$$\underset{s^i \ge 0}{\text{Minimize}} \sum_{i=0}^{4} c^i * s^i + PC^H \quad s.t \quad P\left\{\left[NI^i \ge 0\right] \ge \alpha^i\right\} \text{where } i \in \{0,1,2,3,4\}. \tag{1}$$

This objective function is a linear in nature, it consists of two parts – the first part is the cost of the target base-stock level at each node in the network. The second half of (1) is the penalty cost as a result of information loss at handoff point. (1) indirectly penalizes holding inventory at each location, since higher

s^i corresponds to more inventory of item i (Bollapragada et al. 2004; Niranjan and Ciarallo 2009). The constraints are nonlinear in nature, requiring a desired service level of α^i to be achieved at each node, ensuring that sufficient inventory is held to meet demands with a required level of certainty.

The second half of (1) can be further broken down as (2), which is the sum of expected lost demand cost and expected partial information cost. When the loss of information at handoff > threshold probability (t^P) there is a chance that the entire shipment is rejected by the receiving node until further lab analysis is done on the product, leading to unfulfilled demand. The penalty cost associated to the loss of demand (unfulfilled demand) averaged over all periods results in expected lost demand cost. When the loss of information at a handoff is at the acceptable levels, shipment is not rejected. In order to retrieve the information that has been lost there is an additional time and effort involved, e.g. QA/QC tests, requesting information from the vendor, etc., would be the expected partial information cost, computed as a penalty cost. The penalty cost associated to the loss of information is averaged over all periods results in expected lost information cost.

$$PC^H = E[\text{Lost Demand Cost}] + E[\text{Partial Information Cost}] \cdot \tag{2}$$

Expected lost demand is sum of total lost demand cost for n periods averaged over n periods, similarly expected partial information cost is sum of total partial information (PI) cost for n periods averaged over n periods. A period is a fixed unit time, it can represent day, week, month etc. The two equations are shown below in (3).

$$E[\text{Lost Demand Cost}] = \frac{\sum_{for\ all\ n} \text{Total Lost Demand Cost}_n}{n}; E[\text{Partial Information Cost}] = \frac{\sum_{or\ all\ n} \text{Total PI Cost}_n}{n} \cdot \tag{3}$$

Equation (4) represents the total lost demand cost which is a sum of lost demand cost in every node of the supply chain in a given period n. The lost demand cost in each node is a simple product of the penalty cost and demand in period n. $PC\_LD_n^i$ is the penalty cost of lost demand in node i in period n. Note that if the demand is not lost in a particular node the value of $PC\_LD_n^i$ is equal to zero.

$$\text{Total Lost Demand Cost}_n = \left[\sum_{i=0}^{4} PC\_LD_n^i\right] * \xi_n \cdot \tag{4}$$

Equation (5) represents the total lost PI cost which is a sum of lost PI cost in every node of the supply chain in a given period n. The lost PI cost in each node is a simple product of the penalty cost and demand in period n. $PC\_PI_n^i$ is the penalty cost of lost PI in node i in period n. Note that if 100% of the information is transferred then $PC\_PI_n^i = 0$. If loss of information occurs at an upstream node, it is assumed in this paper that the loss of information cannot be brought back to zero, and the loss can only increase or remain at the same level all the way through to the last downstream node.

$$\text{Total PI Cost} = \left[\sum_{i=0}^{4} PC\_PI_n^i\right] * \xi_n \cdot \tag{5}$$

Equation (6) and (7) define penalty cost for lost demand for nodes 4 to 0. The numerator for all the penalty costs is the actual cost of product at a node. The penalty cost of the product is a function of: i) a constant cost adjustment factor (δ) for lost demand, and a constant quarantine cost adjustment factor (τ) for partial information loss, ii) information received for the product at the receiving node. The value of constant cost adjustment factor is always greater than 0. Since δ and partial information is in the denominator, a value < 1 would imply that there is an increase in the penalty cost per unit compared to the actual cost per unit, and value > 1 would imply a decrease. Since backorders are allowed, penalty cost is in addition to the cost of the product, so for the modeling purposes we think having a cost lower than the cost of product would be appropriate. However this can be changed easily to reflect the other condition. Furthermore, the penalty cost is a function of information received.

$$PC\_LD_n^4 = \frac{C^4}{\delta * P_n^4};\ PC\_LD_n^3 = \frac{C^3}{\delta * \left[P_n^3 * P_{n-l^i}^4\right]};\ PC\_LD_n^2 = \frac{C^2}{\delta * \left[P_n^2 * P_{n-l^i}^3 * P_{n-\left[2*l^i\right]}^4\right]};\ \text{and} \tag{6}$$

$$PC\_LD_n^1 = \frac{C^1}{\delta * \left[P_n^1 * P_{n-l^i}^3 * P_{n-\left[2*l^i\right]}^4\right]};\ PC\_LD_n^0 = \frac{C^0}{\delta * \left[P_n^0 * \min\left\{P_{n-l^i}^2, P_{n-l^i}^1\right\} * P_{n-\left[2*l^i\right]}^3 * P_{n-\left[3*l^i\right]}^4\right]}. \tag{7}$$

At Node 4 information received is based on only one variable (P_n^4), probability of handoff (information received) in period n at node 4. As the product moves downstream the information received will also include the earlier information. E.g. node 2 which is the last part of (6), the denominator includes a product of three probabilities $[P_n^2 * P_{n-l^i}^3 * P_{n-2l^i}^4]$, two upstream nodes' handoff probability and one probability handoff for node 2. Also note that the lead time between the nodes has to be taken into account when the P_n^i is computed, and we see that is reflected in the subscript of P_n^i. The value of the probability of handoff is a value between 0 and 1 and is based on a uniform probability distribution, where a random value is assigned every period. The purpose of using the P_n^i in the denominator is to inflate the cost of penalty proportionally with loss of information. As more information is lost, penalty cost increases. In (7) we see that a minimum function is used to determine the probability of handoff between node 1 and 2, and that is because of the two DCs in one echelon. Although an average or the maximum probability of handoff can be selected, we take a conservative value (lower value).

Similar to the penalty cost function of the lost demand we compute penalty cost for partial information received (acceptable level of information is received for verifying the quality of the received product, and this suggests that the product is not compromised). (8) and (9) are similar to (6) and (7), except $\tau \geq \delta$. The penalty is lower for partial demand received compared to lost demand, since the information lost is at acceptable levels.

$$PC\_PI_n^4 = \frac{C^4}{\tau * P_n^4};\ PC\_PI_n^3 = \frac{C^3}{\tau * \left[P_n^3 * P_{n-l^i}^4\right]};\ PC\_PI_n^2 = \frac{C^2}{\tau * \left[P_n^2 * P_{n-l^i}^3 * P_{n-\left[2*l^i\right]}^4\right]};\ \text{and} \tag{8}$$

$$PC\_PI_n^1 = \frac{C^1}{\tau * \left[P_n^1 * P_{n-l^i}^3 * P_{n-\left[2*l^i\right]}^4\right]};\ PC\_PI_n^0 = \frac{C^0}{\tau * \left[P_n^0 * \min\left\{P_{n-l^i}^2, P_{n-l^i}^1\right\} * P_{n-\left[2*l^i\right]}^3 * P_{n-\left[3*l^i\right]}^4\right]}. \tag{9}$$

Note that when information loss is beyond a certain acceptable level a lost demand occurs. But in some instances the shipment may be accepted 'at risk'. We model this situation using γ_n^i. E.g. node 3 has information loss beyond acceptable level, but it still has a 50% chance of being accepted. However, the product is entitled to pay a penalty cost corresponding lost information. However, the information loss is irreversible as it moves through downstream and thus when the product moves to node 2 it will have an information loss which is less than or equal to the information loss of the product received at node 3.

3.2 Information Sharing

There are typically two types of information sharing – centralized and decentralized. A theoretical structure for these two types of information sharing schemes is shown in Figures 2 and 3, respectively. Probability of information loss is a function of incorrect information transmission and loss of information. It is not clear if information losses are more frequent in centralized or the decentralized system. In a decentralized information sharing environment, the product attribute information is updated initially in the respective server at the firm level, and later necessary information is updated in a central server or sent to manufacturer's server. This leads to a time lag in the system. In order to avoid the time lag, a centralized information sharing is employed (Figure 2), where necessary information is updated in a central server and the manufacturer has access to all the information at any point of time throughout the supply chain. A centralized information update is very crucial for a successful acceptance of the pharmaceutical products by the end customer, due to the sensitive product attributes.

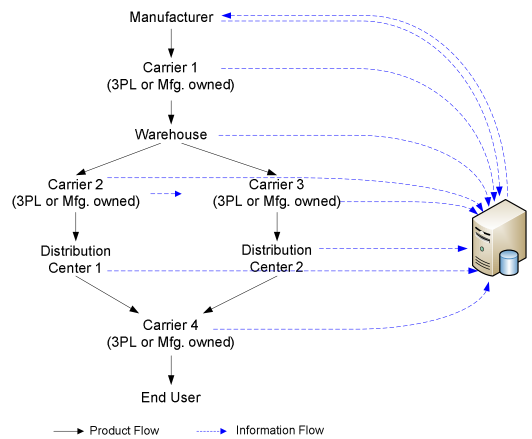

Figure 2: Centralized information sharing.

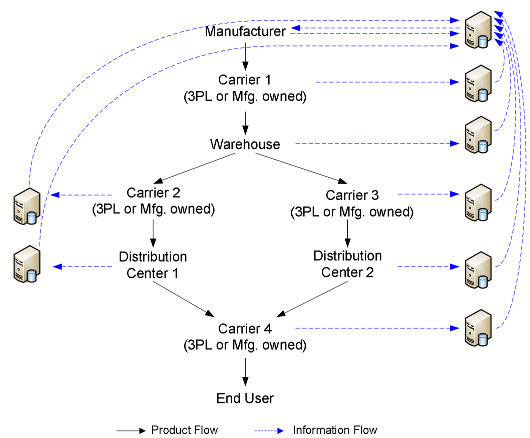

Figure 3: Decentralized information sharing.

In this research paper we only consider a decentralized system. The expected probability of information received at the handoff points is given by (10).

$$E\left[P_H\right] = \frac{\sum_n \left[P_n^0 * \min\left\{ P_{n-l^i}^2, P_{n-l^i}^1 \right\} * P_{n-\left[2*l^i\right]}^3 * P_{n-\left[3*l^i\right]}^4 \right]}{n} \quad 0 \le P_n \le 1 \qquad (10)$$

Equation (10) represents the expected probability of handoffs computed over n periods. The expected value of probability handoff is computed at the downstream node 0, based on the information being received at every handoff from nodes 4 to 0. If the value of P_n ($0 \le P_n \le 1$) is close to one, then very little information is lost or incorrect. $P_n \rightarrow 0$ indicates significant portion of information loss or incorrect during the transmission. Note that if demand is lost at an upstream node due to critical loss of information, there will not be any further loss of information downstream, since there is no product shipped downstream.

We consider a situation where the entire demand for that period is not satisfied, we do not consider the partial demand case. This is a valid assumption as according to the FDA, lapse of product characteristic results in the entire shipment going back to lab for additional tests or being disposed.

3.3 Analytical Equations for Structure Under Consideration

Each node in Figure 1 has a set of update equations for the outstanding orders and on-hand inventory. Dynamic equations associated with each node for the default network is formulated. The equations for other networks can be formulated very similarly. The equations for node 4 are listed below from (11)-(14).

Node 4 (i = 4) – (11) and (12) are part of outstanding orders, (13) and (14) are part of inventory.

$$Y_n^i = Y_{n-1}^i + \xi_n - \min\left\{Y_{n-1}^i + \xi_n, \eta_n^i\right\} \text{ where } i \in \{4\}; \tag{11}$$

$$\eta_n^i = \begin{cases} \left(Y_{n-1}^i + \xi_n\right) * \gamma_n^i & if \left(1 - P_n^i\right) > t^p \\ Y_{n-1}^i + \xi_n & if \left(1 - P_n^i\right) \le t^p \end{cases} \quad \text{where } i \in \{4\}, \gamma \in \{0,1\}; \tag{12}$$

$$NI_n^i = s^i - Y_{n-l^i}^i - \xi_{n-1} - \ldots\ldots - \xi_{n-l^i} \text{ where } l^i = \text{lead time of node i} \quad \text{where } i \in \{4\} \text{; and} \tag{13}$$

$$I_n^i = \max\left\{0, NI_n^i\right\} \text{ where } i \in \{4\}. \tag{14}$$

The outstanding orders for (11) represents the shortages for that node, shortages can occur due to insufficient supply from further upstream. η_n^i represents the supply from upstream, but in this paper node 4 is the starting node the supply from further upstream is raw material. In order to provide a general approach, η_n^i is used as an expression for supply. We assume that the supply is constrained by the loss of information or inaccurate information transmission beyond a certain acceptable level (threshold for loss of information, t^P). If (1-P_n^i) > t^P then the demand at node 4 (ξ_n) will be satisfied with a probability equal to γ. γ = 0 will result in shortage at that node. The penalty cost for lost demand will only be computed when γ = 0, else the penalty cost of partial information will be calculated for that node at that period. We use γ because we feel that loss of information or inaccurate information may not always result in discarding the shipment, there is always a chance of making a judgment even with some loss of information. So there is an equal amount of chance for the shipment to be accepted or discarded. However, the penalty cost would be inevitable, but would be computed under partial information loss. So γ works well here.

If (1-P_n^i) ≤ t^P then the demand is satisfied, but acceptable level of partial information loss could occur. The expression for the capacity is shown in (12). The expression for net and on-hand inventory is shown in (13) and (14). (13) allows inventory to take a negative value, while (14) cannot take on negative values.

Node 3 (i = 3) – (15) and (16) are part of outstanding orders, (17) and (18) represent inventory.

$$Y_n^i = Y_{n-1}^i + \xi_n - \min\left\{Y_{n-1}^i + \xi_n, \eta_n^i, NI_{n-1}^4\right\} \text{ where } i \in \{3\}; \tag{15}$$

$$\eta_n^3 = \begin{cases} \left(Y_{n-1}^3 + \xi_n\right) * \gamma_n^i & if \left(1 - \left[P_n^3 * P_{n-l^3}^4\right]\right) > t^p \\ Y_{n-1}^3 + \xi_n & if \left(1 - \left[P_n^3 * P_{n-l^3}^4\right]\right) \le t^p \end{cases} ; \tag{16}$$

$$NI_n^i = s^i - Y_{n-l^i}^i - \xi_{n-1} - \ldots\ldots - \xi_{n-l^i} \text{ where } l^i = \text{lead time of node i, where } i \in \{3\} \text{; and} \tag{17}$$

$$I_n^i = \max\left\{0, NI_n^i\right\} \text{ where } i \in \{3\}. \tag{18}$$

In the outstanding order (15) for node 3 the supply is constrained by the information loss or inaccuracy, or by the amount of supply from upstream (which is the net-inventory of the upstream node, NI_{n-1}^4). (17)-(18) follow the similar structure as that of node 4.

Node 2 (i = 2) – represents one of the two distribution centers shown in Figure 1. (19) and (20) are part of outstanding orders, (21) and (22) represent inventory. The supply from node 3 has to be allocated appropriately to node 2 and node 1.

$$Y_n^i = Y_{n-1}^i + \xi_n * P_D - \min\left\{Y_{n-1}^i + \xi_n * P_D, \eta_n^i,\ P_S * NI_{n-1}^3\right\}\ ; \quad \text{where } i \in \{2\};\ 0 \le P_D \le 1; 0 \le P_S \le 1 \tag{19}$$

$$\eta_n^2 = \begin{cases} \left(Y_{n-1}^2 + \xi_n * P_D\right) * \gamma_n^i & \text{if } \left(1 - \left[P_n^2 * P_{n-l^2}^3 * P_{n-2l^2}^4\right]\right) > t^p \\ Y_{n-1}^2 + \xi_n * P_D & \text{if } \left(1 - \left[P_n^2 * P_{n-l^2}^3 * P_{n-2l^2}^4\right]\right) \le t^p \end{cases}\ ; \tag{20}$$

$$NI_n^i = s^i - Y_{n-l^i}^i - \left[\xi_{n-1} + ... + \xi_{n-l^i}\right] * \mathrm{P}_D\ ; \text{ and } \quad \text{where } l^i = \text{lead time of node i};\ i \in \{2\} \tag{21}$$

$$I_n^i = \max\left\{0, NI_n^i\right\} \quad \text{where } i \in \{2\}\ . \tag{22}$$

Equation (19) represents the outstanding orders for node 2, includes the proportion of demand (P_D) that comes from DC1. The DC1 (node 2) is only responsible for the fraction of the demand, and not the entire demand, hence $0 \le P_D \le 1$. Similarly the supply from the upstream node 3 is also split up based on the proportion of supply (P_S) and $0 \le P_S \le 1$. For brevity we use a simple 50% split of the demand and supply. This allocation can be changed based on other allocation policies like the proportional, lexico-graphic, and priority based allocation. (20)-(22) are very similar to the earlier nodes.

Node 1 (i = 1) – represents the other distribution center. The equations for node 1 are very similar to node 2. (23) and (24) are part of outstanding orders, while (25) and (26) represent inventory.

$$Y_n^i = Y_{n-1}^i + \xi_n * (1 - P_D) - \min\left\{Y_{n-1}^i + \xi_n * (1 - P_D), \eta_n^i,\ (1 - P_S) * NI_{n-1}^3\right\} \text{ where } i \in \{1\}; \quad 0 \le P_D \le 1; 0 \le P_S \le 1 \tag{23}$$

$$\eta_n^1 = \begin{cases} \left(Y_{n-1}^1 + *\xi_n * (1 - P_D)\right) * \gamma_n^i & \text{if } \left(1 - \left[P_n^1 * P_{n-l^1}^3 * P_{n-2l^1}^4\right]\right) > t^p \\ Y_{n-1}^1 + \xi_n * (1 - P_D) & \text{if } \left(1 - \left[P_n^1 * P_{n-l^1}^3 * P_{n-2l^1}^4\right]\right) \le t^p \end{cases}\ ; \tag{24}$$

$$NI_n^i = s^i - Y_{n-l^i}^i - \left[\xi_{n-1} + ... + \xi_{n-l^i}\right] * (1\text{-}\mathrm{P}_D)\ ; \text{ and } \quad \text{where } l^i = \text{lead time of node i};\ \text{where } i \in \{1\} \tag{25}$$

$$I_n^i = \max\left\{0, NI_n^i\right\} \text{ where } i \in \{1\}\ . \tag{26}$$

Node 0 (i = 0) equations are very similar to node 4 and 3, with an exception that the supply is a sum of supplies from node 1 and 2, essentially the addition of two net inventories of upstream nodes in (27). (27) and (28) are part of outstanding orders, (29) and (30) represent inventory.

$$Y_n^i = Y_{n-1}^i + \xi_n - \min\left\{Y_{n-1}^i + \xi_n,\ \eta_n^i, NI_{n-1}^2 + NI_{n-1}^1\right\} \text{ where } i \in \{0\}\ ; \tag{27}$$

$$\eta_n^0 = \begin{cases} \left(Y_{n-1}^0 + \xi_n\right) * \gamma_n^i & \text{if } \left(1 - \left[P_n^0 * \min\left\{P_{n-l^0}^1, P_{n-l^0}^2\right\} * P_{n-2l^0}^3 * P_{n-4l^0}^4\right]\right) > t^p \\ Y_{n-1}^0 + \xi_n & \text{if } \left(1 - \left[P_n^0 * \min\left\{P_{n-l^0}^1, P_{n-l^0}^2\right\} * P_{n-2l^0}^3 * P_{n-4l^0}^4\right]\right) \le t^p \end{cases} ; \tag{28}$$

$$\begin{aligned} &NI_n^i = s^i - Y_{n-l^i}^i - \xi_{n-1} - \ldots\ldots - \xi_{n-l^i} \\ &\text{where } l^i = \text{lead time of node i; where } i \in \{0\} \end{aligned} \quad \text{; and} \tag{29}$$

$$I_n^i = \max\left\{0, NI_n^i\right\} \text{ where } i \in \{0\} \;. \tag{30}$$

4 PROPOSED SIMULATION

A simulation based optimization approach using two methods are planned: i) using ARENA with OptQuest, ii) Infinitesimal Perturbation Analysis. Figure 4 shows a flow chart that uses ARENA. A design of experiments will be used to comprehensively cover all the product attributes, network structures, and other parameters. Overall cost associated with different cold chain multi-echelon networks will be studied under stochastic demand and probabilistic information loss/accuracy conditions.

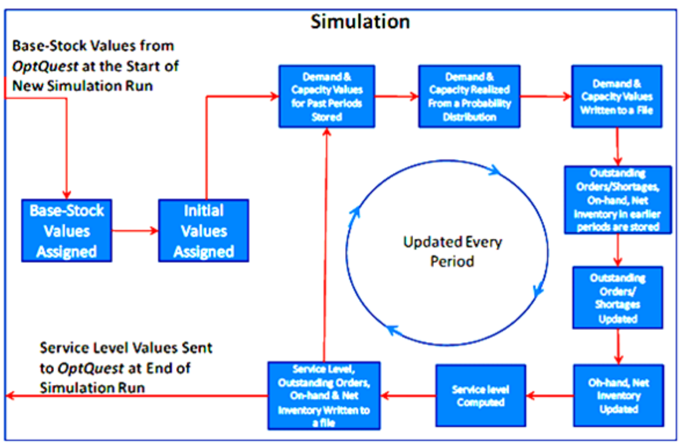

Figure 4: Proposed simulation based optimization.

ARENA is used to update the equations stated in the previous section, all the decision variables including the objective function and constraint is defined in OptQuest, which is a scatter search based optimization tool in ARENA. Upper and lower bound values of all the decision variables (base-stock levels) is defined in OptQuest. A set of values for the decision variables is initially obtained from OptQuest, these decision variable values are used by ARENA and the simulation (updating the equations) run for certain predefined periods, at the end of simulation the service level value is fed as an input to OptQuest. Depending on the service level value a new set of values for decision variables, e.g. outstanding orders, on-hand inventory, etc. is fed back to ARENA.

5 PROPOSED NUMERICAL ANALYSIS

Design of experiments approach will be used to understand how factors influence the supply chain costs. The following factors were of particular interest:

- Constant cost adjustment factor (δ) for lost demand;

- Constant quarantine cost adjustment factor (τ) for partial information loss;
- Threshold probability (t^P);
- Probability of information received at node i in period n (P_n^i); and
- Supply chain ownership cost.

A 2-factorial design is selected to assign each factor high and low levels for the first four factors. Table 1 provides the details.

Table 1: 2-factorial design.

Factors	Low	High
Cost adjustment factor (δ) for lost demand	5	10
Quarantine cost adjustment factor (τ) for partial information loss	5	10
Threshold probability (t^P)	0.3 (30%)	0.15 (15%)
Probability of information received at node i in period n $\left(P_n^i\right)$	Unif(0.7, 1)	Unif(0.85, 1)

A 3-factorial design (low, medium and high) is selected for the supply chain ownership. A low ownership cost results in one single organization being the owner of the entire cold chain. Medium ownership cost occurs when the manufacturing center and the warehouse are owned by one organization, whereas the DC and the retail stores owned by a second organization. High ownership cost occurs under a situation where manufacturing, warehouse, DC and retail stores are owned by different organizations.

For all the numerical scenarios, a two-period lead time between the echelons is assumed. The demand for the end product is based on a normal distribution. Four demand instances are considered: i) LOW product demand and LOW demand Coefficient of Variability (CV), ii) LOW product demand and HIGH demand CV, iii) HIGH product demand and LOW demand CV, iv) HIGH product demand and HIGH demand CV. A LOW product demand is a value of mean demand between 10 and 15 units, HIGH product demand is a value of mean demand between 30 and 35 units (approximately 3x the LOW product demand). LOW demand CV corresponds to CV = 0.1, whereas HIGH demand CV corresponds to a value equal to 0.4. Each instance includes four scenarios with varying demand values, the demand values are randomly selected using MSEXCEL.

Table 2 provides all the numerical scenarios. The best base-stock levels, safety-stock levels and total cost for a given numerical scenario is computed under each factor considered in the 2-factorial design. OptQuest determines the values of the decision variable (base-stock values for each node) for each run based on a pre-specified upper and lower bound base-stock values, these values are assigned to corresponding variables defined in ARENA. Each simulation run consists of 1500 periods, and in each period the values for demand is drawn from normal distributions with the parameters specified by the experimental design. A target service level of 90% is used for each node. At the end of the simulation for 1500 periods the service level values are returned to OptQuest along with the penalty cost value. OptQuest then determines the base-stock level values for next round of 1500 periods based on the feasibility of the constraints, and thus automatically determines if the value of a certain node's base-stock level needs to increase or decrease. This process continues until there is no further improvement in the total cost for several runs. The best base-stock levels for a given numerical scenario along with the total cost is determined for a given service level.

Table 2: Demand values.

Instance 1 **Demand = LOW** **CV =LOW**	**Instance 2** **Demand = LOW** **CV =HIGH**	**Instance 3** **Demand = HIGH** **CV =LOW**	**Instance 4** **Demand = HIGH** **CV =HIGH**
1. Norm(15, 1.5)	5. Norm(15, 6)	9. Norm(30, 3)	13. Norm(30, 12)
2. Norm(11, 1.1)	6. Norm(11, 4.4)	10. Norm(34, 3.4)	14. Norm(34, 13.6)
3. Norm(14, 1.4)	7. Norm(14, 5.6)	11. Norm(33, 3.3)	15. Norm(33, 13.2)
4. Norm(12, 1.2)	8. Norm(12, 4.8)	12. Norm(35, 3.5)	16. Norm(35, 14)

6 CONCLUSION AND FUTURE WORK

Maintaining pharmaceutical product attributes is very critical from quality and authentication standpoint for cold chains. Furthermore, it is mandatory from regulatory perspective that material attributes are monitored, recorded and reported in a timely and accurate manner. Failure to comply with these regulations can result in penalties to the players involved in the supply chain. These challenges, along with those encountered in traditional supply chains, increase the complexity in managing pharmaceutical supply chains. Consequently, costs of such chains can be considered to be a function of aspects belonging to the traditional supply chain, in addition to (timely and accurate) information transmitted regarding the component attributes.

In this paper, a simulation model associated with one cold chain multi-echelon network is developed under stochastic demand and probabilistic information loss/accuracy conditions. Dynamic equations for the network are formulated for the particular network structure under consideration. Currently numerical analysis using Simulation based optimization using OptQuest is being conducted. Simulation based optimization will be conducted using IPA approach once the insights are about the model are found using OptQuest. Recommendations to reduce cold chain costs will be provided after performing sensitivity analysis within cold chain network for various parameters, specifically using supply chain ownership costs as part of the current analysis.

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