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"Application of Operation Research in the Pharmaceutical Industry"

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Abstract

Management science, according to Stafford Beer, may be called as the business use of operations research. According to Frederick S. Hillier, operation research is applied to problems that concern how to conduct and coordinate organizational operations. Medicine, healthcare and pharmaceuticals are thriving industries in the 21st century, the relevance of which is bound to increase in the near future. The pharmaceutical industry is one with activities being undertaken on a massive scale, involving expertise of several other fields and sectors. When their products, which mainly include chemical drugs, are discovered, developed, made and marketed, it involves the use of operation research in several ways to make the processes more efficient. Operation research is mainly used to make this industry more profitable, as well as to make their activities easier and faster. Through the study of this paper, it is expected to understand how relevant the application of operation research is to the pharmaceutical industry, with special emphasis on operations that do not directly relate to their production, such as but not limited to supply chain management, inventory management, financial management and project management, to what extent are such methods adopted, and whether it can be applied to a small pharmaceutical company (case study) that currently outsources most of its operations.

Introduction

Pharmaceutical processes are complex, which involves many steps, agencies, ministries and manufacturers. The sum total of these activities is a huge task to manage, and pharma companies deploy a number of resources and manpower to manage these activities.

[Existing government policies, rules and regulations for procurement as well as institutional structures are frequently inadequate and sometimes hinder overall efficiency in responding to the modern pharmaceutical market. There are many steps in the procurement process of pharmaceutical raw materials, partially finished goods and finished drug products. No matter what model is used to manage the procurement and distribution system, efficient procedures should be in place: to select the most cost-effective essential drugs to treat commonly encountered diseases; to quantify the needs; to pre-select potential suppliers; to manage procurement and delivery; to ensure good product quality; and to monitor the performance of suppliers and the procurement system. Failure in any of these areas leads to lack of access to appropriate drugs, and wastage.

A study conducted by the Department of Personnel and Administrative Reforms in India has revealed that not only does the quantity of medicines received fall short of the requirement but also the supply is often erratic. Of the various explanations for non-availability of even simple medicines in the third world countries, a large number are related to materials management.

In many public supply systems, breakdowns regularly occur at multiple points in this process, which results in fragmented supply chains. In addition to it, erratic funding by the government and donor agency with conflicting procurement needs poses another issue for the industry.

Even if appropriate policies and procedures are in place, lack of properly trained staff in key positions can doom any procurement system to failure. While effective training programmes can remedy this problem, in many supply systems there is limited access to training in good procurement practices. Also unattractive public sector salaries and lack of career development tend to restrict capacity to attract and retain qualified staff.][1]

Operation on such a large scale brings the possibility of loss in efficiency, as well as the situation to make informed, optimal decisions regarding choices, and the right mix of resources and products. This emphasizes the need for planning, designing and organizing the pharmacy in a manner that results in efficient clinical and administrative services. It creates a need for pharmaceutical companies to adopt Operation Research techniques to maximize the efficiency of their output.

Database Management Systems

[The industry has developed a set of tools and databases specifically for pharmaceutical operations, focusing on benchmarks. Pharmaceutical Operations Benchmarking of Solids (POBOS) allows companies to benchmark manufacturing costs and productivity to comparable peers for many different areas, including multiple fill/finish technologies, synthesis of active pharmaceutical ingredients (API), and production of biologics. POBOS is a database consisting data of above 50% of the top global pharma companies. This benchmarking system is used by the companies to present their position in the competitive market in a simple, streamlined manner using industry standards in arenas such as but not limited to manufacturing cost, productivity, supply chain, purchasing and quality performance.][2]

Strategic and Operational Portfolio Management

For better application of pharmaceutical analysis to improve business, pharmaceutical companies need to manage a portfolio of different products and their development. Just managing one product is already complex. However relying on one product alone to make a pharmaceutical company profitable and efficient in operations would be unacceptably risky. Thus using operations research in their operations is very important and vital for the companies.

[Blau et al. in his paper in 2000 aimed to support the process of product selection and test planning while managing risk effectively. The development activities are modelled as a probabilistic activity network, where each activity has a time, precedence relations, resource requirements and probability of success. Risk is defined as the adverse consequences of exposure to uncertainty, and in this context is usually related to the premature withdrawal of a candidate drug. The risk of a set of decisions must be balanced against the potential reward. In this case, the potential reward is the expected financial returns of drugs that do make it through the development process. The risk/reward ratio can then be used to compare different drug candidates. A screening process removes any obviously unpromising candidates, and then the remainder must be sequenced through the development pipeline. A heuristic approach using simulation with local rules in response to trigger events (e.g. failure of a test) is employed. This aims to process tasks as quickly as possible and although there is no guarantee of not violating resource constraints, these violations are usually not large.][6]

Manufacturing

[Total Productive Maintenance (TPM): TPM is a manufacturing program designed to maximize the effectiveness of a manufacturing site's equipment and to improve its overall efficiency throughout the equipment's lifetime by motivating and involving the entire workforce across all hierarchies. To achieve maximum effectiveness of its production system, a manufacturing site has to prevent failures, defects, and dysfunctions of its equipment, i.e. completely eliminate wastes and losses during operations. A manufacturing operational excellence in pharmaceutical site may utilize the TPM philosophy and its strong positive influence on various performance dimensions to strengthen a facility. Maintenance management within TPM programs is usually divided into short-term activities and long-term efforts. The latter typically involve different departments throughout the organization and comprise the design of new equipment and stepwise reduction of sources of equipment downtime. Short-term maintenance elements are focused on site level and comprise autonomous and planned maintenance tasks.][15]

Quality, Compliance, Remediation

[In a world of increasing complexity and regulation, quality is an often untapped source of competitive advantage. Superior quality and flawless compliance can help companies dramatically reduce quality-related costs, improve their brand perception, and improve revenues. Use of Operation Research in their functions helps companies achieve required quality levels. Models help companies achieve significant and sustainable improvement in their quality performance, customer satisfaction, and regulatory compliance. The areas of quality expertise that Operation Research helps achieve is development of quality and compliance strategies, quality performance and cost benchmarking, optimizing the quality management system (QMS), delivering compliance and remediation services, and fostering a quality culture.][2]

Supply Chain Management (SCM)

[Operation Research in pharmaceuticals helps companies understand the customer's perspective to develop an end-to-end view of the supply chain, working with companies to define strategy, redesign distribution networks of medicines, benchmark performance, identify problems during distribution, improve service levels, manage risk associated with transport and stock piling, reduce backorders, and lower inventory.][2]
[It starts with process development and plant design. Conceived by Linninger, Ali, and Stephanopoulos (1996), it involves a hierarchical approach, with the emphasis on the use of knowledge bases and material balancing at every development level to choose and assess options. The focus is particularly on synthesising routes and developing processes with low environmental impacts.][11]

Retrospective Optimization Integer Programming **(**ROIP) approach is used in biopharma to maintain optimum levels of inventory. ROIP uses an integer program to optimize inventory parameter settings along a sample path. [While very complex supply chain settings lead to big, difficult to solve integer programs, an approximate approach based on stochastic gradient search methods can be used. A numerical study demonstrates that a hybrid approach that combines integer programming with stochastic gradient search can reduce solution times from over 20 hours to just a few seconds while finding solutions that are a fraction of a percent away from the solutions found by the integer program.][12]

[Eppen, Martin, and Schrage (1987) developed a "risk factor" based on expected downside risk. This gives a measure of the failure to meet a certain target profit. The risk factor is easiest understood in a discrete scenario context. It is calculated as:

$RF = k{:}r_k \leq r_0$
$(Pr[k])(r_0 - r_k)$

RF is Risk Factor
k is Scenario Index
r_k is Risk in Scenario k
Pr[k] is Probability of Scenario k

An upper bound can then be enforced on Risk Factor. By tightening the constraint on expected downside risk, it is possible to bring alternative solutions to the attention of the decision-makers.][10]

[With the help of Operation Research, companies have developed a thorough understanding of external suppliers and contract management organizations (CMOs), including their capabilities and typical costs. Through market knowledge and experience, they have helped clients capture both immediate and sustainable value in multiple projects. The approach used in Operation Research entails working with clients to create a comprehensive external supply strategy, segment suppliers, develop metrics for vendor performance, and establish clear management guidelines to optimize value from third-party suppliers.][2]

[Many pharmaceutical companies have now settled on using preferred partnership deals with Contract Research Organisations (CROs) to deliver their clinical study programmes. They conduct these programmes as they need to maintain relationships with multiple clients to make them responsive customers. It also gives them access to a talent pool which is considerably bigger than one which a single Pharmaceutical Company could have.
CROs help understand the potential for cost savings if the activities were to be outsourced.][14]

Use of ABC and VED Analysis

The use of operations research helps in shop-floor production efficiency through lean manufacturing methods.
[Always Better Control (ABC) analysis is a method of classifying items or activities according to their relative importance. It is also known as "separating the vital few from the trivial many" because, for any group of things that contribute to a common effect, a relatively few contributors account for a majority of the effects. The limitation of ABC analysis is that it is based only on monetary value and the rate of consumption of the item. ABC analysis is often used by pharmaceutical companies to realize which production methods are cost effective and safe to undertake. It also helps them understand the product mix that is easy to produce with the given resources.

Another technique, the Vital Essential and Desirable (VED) analysis is based on critical values and shortage cost of the item. Based on their criticality, the items could be classified into three categories: vital, essential and desirable.

A combination of ABC and VED analysis (ABC-VED matrix) can be gainfully employed to evolve a meaningful control over the material supplies. Category I includes all vital and expensive items (AV, BV, CV, AE, AD). Category II includes the remaining items of the E and B groups (BE, CE, BD). Category III includes the desirable and cheaper group of items (CD). It leads to a better understanding of production methods that companies can adopt to meet drug demands by optimising their supplies and assets.][3]

Resource and Task Management

[Jain and Grossmann (1999) developed a methodology for the sequencing and scheduling of testing tasks under resource constraints. In this approach, each product has a specified set of testing tasks. Each task is characterised by duration, cost, precedence constraints, resource requirements and probability of success. A task may be outsourced at a higher cost; in this case no internal resources are required. The income associated with a product is given as a function of the time of launch in the market. The formulation developed is conservative and always feasible in that the resource constraints are always enforced, regardless of the probability of a task not actually taking place. The cost component is modelled as an expected cost. This ensures that the effect of starting tasks earlier than necessary is modelled, i.e. that later tasks may not actually take place due to the failure of the earlier one.][4]

[In a nutshell, the proposed MIP-based solution strategy has as a core MIP scheduling framework and consists of two major procedure steps:

(i) the constructive step, and

(ii) the improvement step.

The objective in the constructive step is the generation of a feasible schedule of drug production in short amount of time. Afterwards, this schedule is gradually improved by implementing some elaborate rescheduling techniques and making adjustments to machinery setup, in the improvement step.

As a sequence, the generation of feasible and fairly good schedules in reasonable computational time is favoured. This works on principles similar to Assignment problems, however, it involves more number of variables and sequencing them in a specific way to achieve optimality.

I. Constructive Step

- Insert orders one by one using an insertion creterion and solve MIP
- By fixing allocation and sequencing variables for previously scheduled orders.
- When all orders have been inserted, a feasible solution is obtained

II. Improvement Step

- Realize recording until no improvement appears.
- Take out and insert orders again one by one.
- Select to reschedule order with better OF.
- No further improvement, stop algorithm and report solution

][5]

[Subramanian, Pekny, and Reklaitis (2001) extended this work to take explicit account of the resource requirements of the problem. The problem statement is generalised in that more uncertain variables in the problem are considered and include task processing times, task resource requirements, task success probabilities, task costs and market returns.

They make the point that a single-level mathematical programming problem cannot hope to capture all these features. On the other hand, Discrete-Event Dynamic Systems (DEDS) techniques cope well with the stochastic elements, but require local, myopic rules to resolve conflicts or make choices as they arise. The authors therefore developed an integrated optimisation–simulation framework (SIM–OPT), where a DEDS simulator reverts to an optimisation layer (with different degrees of optimisation) to resolve conflicts or make

choices such as task sequencing. The optimisation layer is an MILP which is updated by the latest status of the plant.
The results show that using optimisation far outperforms the typical local rules used in classical DEDS. By repetitive simulation, the statistical trends can be tracked and answers to questions about corporate policy (particularly in relation to risk and resourcing) can be obtained.][7]

[The Multi-Mode Resource-Constrained Project Scheduling Problem (MRCPSP) is a generalization of the single-mode RCPSP (SR-CPSP) where an additional mode-assignment step has to be considered. The aim is to find the best mode-assignment for a number of jobs subject to non-renewable resource constraints such that the optimal schedule for the resulting SRCPSP (if existing) optimizes a specific objective function.][16]

Capacity Planning

[Rotstein et al. (1999) used a scenario tree to capture the outcomes of the trials, and use a two-stage stochastic programming with recourse formulation to model the problem. The 'here-and-now' decisions related to immediate capacity expansions and the 'wait-and-see' decisions depend on trial outcomes and include decisions for further capacity expansions, plant or product abandonment and production and inventory planning. They show how different options can be compared using a number of metrics, including expected net present value (NPV), the probability of the NPV being negative, the worst case scenario, the total demand met of all the potential products and the total demand met of the products chosen from the portfolio.

Gatica, Shah, and Papageorgiou (2001, 2002a) concluded, that when different products are at different stages in their life-cycles, a multistage stochastic optimisation problem is used where completion of each stage reflects completion of a clinical trial. This trial uses four outcomes (failure, low, target and high) based on typical practices in industry. This means that four scenarios are required per stage. and for a problem with N stages (i.e. N products in trials), there is one scenario in the first stage (reflecting products currently in the market with well forecasted demands), four scenarios in the second stage (reflecting the four possible outcomes for the first pipeline product to come out of trials), 16 in the third stage (the combinations of outcomes for the two products to complete trials) and so on, until the final stage which has 4N scenarios. Each scenario is associated with possible capacity expansions and production and inventory planning variables and constraints, so the problem becomes a large scale stochastic programming problem with integer and continuous decisions. It is solved as a large MILP.

Since this approach is very complex, Gatica, Papageorgiou, and Shah (2002b) extend it by using a scenario aggregation procedure similar to that of Clay and Grossmann (1997) to enable the solution of larger problems.][8]

[Maravelias and Grossmann (2001) aimed to optimize a performance measure (expected NPV) for the process as a whole. This bridges the gap between the two problems and aims to ensure that the company is ready to produce a product once testing is complete (if the product is successful). The testing process is modelled as a set of tasks with technological precedence constraints, durations and resource requirements. The tasks have two possible outcomes, success or failure. All tasks other than process development may be outsourced if internal resources do not suffice. Since the method is to be applied at any time in the company's operation, it takes account of the fact that different products will be at different stages in their life-cycle. If at any stage a product fails a test, it is abandoned. The manufacturing process is assumed to have existing capacity as well as potential new capacity. However, production only takes place if a product successfully completes its tests.][9]

Inventory Modelling

Mathematical Modelling is used for inventory modelling. [Kelle et al. focuses on pharmaceutical inventory management in a single care unit, and propose a multi-product inventory management model using an (s, S) policy for each product. The full model with consideration of product volume and space constraints proves difficult to solve, so the authors develop several simplified models. The authors demonstrate that implementing these simplified models can result in reduction in inventory expenditures of up to 80%][13]

Case Study

Europa Biocare Pvt. Ltd. is a Mumbai based business to business pharmaceutical project management services company promoted by a team of highly qualified and experienced international pharmaceutical experts under the leadership of Mr. R.A.S. Mani Iyer.
They outsource the manufacturing of bulk drugs, disposables and raw materials for projects as per norms and requirements of the World Health Organization, Good Manufacturing Practices and United States Food and Drugs Association and offer turnkey consultancy services, technology transfer and merger & acquisitions consultancy services.

Turnkey Consultancy: Europa provides turnkey consultancy services which include conceptualization and designing of a new plant, as well as existing plant, its construction, setting up manufacturing facilities and its commissioning.
Master Planning: They help their clients to formulate a plan to meet their strategic goals and recognize opportunities for innovation. Concept designs and master plans serve as a guideline for basic and detailed engineering development in order to find solutions for fulfilling the basic functional requirements at the lowest life cycle cost.
Facility Engineering: It involves the study of various alternative schemes to arrive at the most suitable one, keeping in view the functional economical and an esthetical aspect. It also includes preparation of machinery layout drawing as per the Process Consultants' guidelines.
Installation & Commissioning: They provide commissioning documents that verify proper installation, operation at start-up, functional performance, and turnover of facilities, systems and equipment. Commissioning services include SAT (Site Acceptance Test), to ensure all systems are supplied in specified condition.

Mergers & Acquisitions: Europa provides end to end merger & acquisition services to small and medium size enterprises and helps them to find the right partners, growth opportunities, diversification options, funds and good business opportunities. They help in searching the targets/ buyers, deal advisory, valuation and due diligence.

With such widespread operations not only related to manufacturing, it is essential that Europa adopt certain techniques to improve their efficiency in aggregating services and products and outsourcing activities.
Through database management systems such as POBOS, it can choose the right vendors and plants to get their orders manufactured and processed, as well as deduce optimum supply chains and acceptable quality levels by customers.
Europa has a host of different products in different sub categories that may become a difficult task to prioritize, if there are may arise a situation of limited resources. In this scenario, risk measurement and obtaining risk/reward ratios seems to be an ideal method for them to make better decisions. At the same time, they should make use of ABC-VED analysis to conclude what are the best activities to be undertaken to achieve their goals. They should also urge their partner manufacturing sites to use TPM philosophies to prevent failures, defects and wastage and losses during operations.
Their operations result in finished products to retailers across the world. In the export business, customer satisfaction is vital, and this is primarily achieved by supplying good quality products. Through Quality Management Systems, delivery compliance and remediation services, a quality benchmark can be set and maintained by them in the competitive market.
Their inflow of orders can also be managed by using MILP methods and computerized scheduling to rank which orders are better to be undertaken.

It is advisable that they make use of CROs to understand upto what extent should operations be outsourced. CROs can help them achieve a wider customer base in foreign countries, where the client is assured of quality and feels satisfied with the finished products.
While aggregating tasks, there are several perspectives that the company needs to look from while devising the perfect sequence and extent to which processes are outsourced and conducted. Making use of DEDS can help them judge risks associated with their hired help and vendors while resourcing materials, production, packaging of drugs as well as their export.

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