Manufacturing

Flexibility: a Critical Factor in Today's Pharmaceutical Manufacturing Industry

In today’s changing industry environment, integrated planning and scheduling tools are central to developing the manufacturing flexibility necessary for companies to remain competitive.

Times are changing in the pharmaceutical market and, as a result, the industry is facing a new set of challenges which are forcing companies to rethink how they approach supply chain and manufacturing practices. The industry has long been characterised by high R&D and production costs — particularly in biotechnology — heavy regulations, low operational efficiency, high inventories and long cycle times. Until recently, the industry has managed to sustain high profit margins in spite of these challenges. However, this is no longer the case as numerous pressures — including tightening government regulation, counterfeiting and competition from generics, as well as a shortening of patent protection times and scientific-technical evolutions — are having a detrimental impact on profit margins.

As the pharmaceutical industry faces an increasingly complex environment, new supply chain and operating models have become essential. In this article, we consider how flexible and lean manufacturing and supply chain strategies have become critical for pharmaceutical companies wishing to remain competitive in today’s changing landscape.

NEW TECHNIQUES FOR A NEW WORLD

Lean manufacturing, demand-driven manufacturing and demand-driven supply chain techniques have all become increasingly crucial to maintaining revenue for all types of manufacturers. Indeed, in recent years, companies such as AMR Research have promoted best practices using these techniques, which involve a better synchronisation between manufacturing execution, supply chain processes and demand sensing.

Companies in industries such as electronics, furniture and telecommunications have successfully used lean manufacturing to improve their operations. Unsurprisingly, the most successful lean implementations are found in the discrete industries characterised by high volume, repetitive operations and assembly lines. Due to these characteristics, lean is a strong fit for overcoming many of the challenges faced by these companies.

In order for the pharmaceutical industry to effectively take advantage of these techniques, it must look to these industries and learn from their best practices for introducing flexibility into manufacturing and the supply chain. Business processes and technology that enable companies to be more flexible and agile will become increasingly important in ensuring that pharmaceutical companies remain profitable and grow in the face of increasing complexity.

HOW TO IMPLEMENT LEAN TECHNIQUES TO IMPROVE OPERATIONAL FLEXIBILITY

The main objective of lean manufacturing is to provide the best possible service to customers through the elimination of all forms of waste. Waste can take the form of material or energy waste, inventory, defects or wasted capacity. In order to avoid waste, manufacturing execution must be tightly synchronised with supply chain plans and customer orders so that the ideal throughput of the manufacturing process is equal to customer demand.

Lean techniques have clearly been driven by the requirements of assembly line manufacturing. Achieving similar results in different manufacturing environments requires an understanding of the key lean principles, which can be listed as follows:

✦ Take a holistic view: The production environment needs to be optimised as a whole, with the aim of closely coordinating operations that are physically separated.

✦ Attention to detail: Operational details are strategically important in lean manufacturing. The focus on set-up reduction is a good example. Instead of taking set-ups as a fixed constraint of the system, engineers try to reduce the set-up time so that non-productive operations are minimised.

✦ Control Work in Progress (WIP): Controlling WIP is an important objective achieved through the use of Kanban cards. The key idea is to change the manufacturing process from a ‘push-based’ manufacturing process to a ‘pull-based’ one.
Reduce cycle time: Reducing cycle time is a key objective in lean manufacturing. It is achieved by reducing set-ups and delays, coordinating machine maintenance with production operations and optimising space in order to better utilise workers, equipment and workstations.

Not only can it be very challenging to implement lean techniques in the pharmaceutical industry, but worse, it can generate very poor manufacturing performance if not implemented correctly. For example, reducing lot sizes in this industry may lead to waste through low utilisation of tank capacity.

More generally, it is not clear how to implement a pull strategy in a production process characterised by strong economies of scale and/or requires batching. If raw materials and intermediate products are produced and stored in tanks, it becomes very difficult to implement pull scheduling and a one-piece flow process (that is, a process in which each product moves through the process one unit at a time). Similarly, the Kanban concept is appropriate for discrete manufacturing, but hard to implement in the pharmaceutical industry. Furthermore, quick changeovers can be very ineffective, hard to implement in the pharmaceutical industry.

Although traditional lean techniques cannot be applied to the pharmaceutical industry, lean principles can be applied to identify requirements for implementing effective manufacturing strategies:

- **Take a holistic view:** Sequencing and scheduling decisions must be made by looking at their impact on both resource efficiency and inventory levels, and including information about raw materials, intermediates and finished goods.
- **Attention to detail:** Operational details must be taken into account when generating production plans and schedules. Building a plan that ignores key manufacturing constraints – such as tank capacities, cleaning rules or sequence-dependent changeover times – will generate continuous adjustments to the plan. Unfeasible plans generate many unplanned changes, which create more changeovers and waste. Additional changeovers generate loss of capacity and inventory shortages, which in turn generate expedite orders and new unfeasible plans.
- **Control WIP:** Controlling and reducing WIP can be achieved by carefully coordinating intermediate product production, finished product production and demand signals.

Reduce cycle time: Cycle time includes two components: wait time and processing time. Wait time is reduced by better coordinating the flow of material (for example, intermediate products and finished goods), while processing time reduction is achieved through carefully optimising the balance between changeover times and costs, and inventory costs.

These requirements suggest that there is a need for effective optimisation methods that take a holistic view of the production process and balance the various trade-offs while considering all business constraints. Such methods also provide planners with enough flexibility to easily and effectively modify production plans (see panel below).

**EXTENDING FLEXIBILITY TO THE DESIGN OF PLANTS: THE BIOTECH EXAMPLE**

The revenue of biotech companies in the past 10-15 years has experienced exponential growth, but profits have not always met expectations (1). In fact, not only are R&D costs extremely high, but building biotechnology facilities is also very expensive and these facilities are often inflexible as they tend to be designed for a single product. Manufacturing processes in biotech are extremely

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**Results and impact on flexibility using ILOG plant PowerOps**

Following an implementation of ILOG’s planning and scheduling solution, Plant PowerOps (PPO), the results were analysed in terms of inventory coverage, production smoothing and operational efficiency. The results clearly demonstrated a strong reduction of inventory excesses (which almost went down to zero) and deficits. These results were achieved by finding the right balance between inventory costs and changeover costs under tight resource capacity constraints.

In terms of manufacturing performance, the results obtained illustrated a significant improvement in operational efficiency, which was improved by values ranging from two to five per cent. The total time due to non-productive activities – such as cleaning-in-place and changeover – was reduced by 20 to 40 per cent. The reduction in changeovers and cleaning, and the increase in operational efficiency are clearly linked. In fact, operational efficiency is defined as the ratio between the operational time and net production time, and the reduction of changeovers and cleaning improves a reduction in operational time without impacting the net production time.

Production smoothing was also improved: the production frequency of the optimised plan was significantly more stable than the frequency of the manual plan, and the production variability (in units) was also reduced.

Among the many benefits of this implementation, the two that most directly affect manufacturing flexibility are increased operational efficiency and faster rescheduling.

Increasing operational efficiency means that the plan is able to produce the same output of product using resources for a shorter amount of time, thus creating “buffers” of resource capacity. These capacity buffers strictly define manufacturing flexibility. In fact, they can be used in many ways:

- To increase volume without making heavy capital investment
- To accelerate product launches and react to market changes
- To reduce the impact of production variability

The ability to increase throughput without making any changes to the production facility or production process is particularly important for the biotech industry. In this industry, equipment is very costly, changes in production may have to go through FDA approval and product stock-outs are often unacceptable.

In general, the ability to increase throughput without committing to heavy capital investment is very important in situations where the market evolution is unknown. In other words, any technology that reduces the magnitude of capacity increments while meeting market requirements provides flexibility to the system.

It is also easy to see how reducing planning and scheduling cycle times from one to two days to just a few hours directly affects manufacturing flexibility. If planners are able to generate a feasible plan in a few hours, they will be better able to respond to market changes or business requirements, and also react better to production problems, for example, if a batch is segregated.
complex, involving cell growth in bioreactors, a sequence of purification steps in chromatography columns and filtering equipments, and also involving manufacture of the media and buffer preparations necessary in different processing steps. All these different steps must be tightly coordinated and involve shared resources, such as labour and equipment for cleaning-in-place. In the last few years, there has been increasing recognition that both manufacturing operations and plant and process design are key to bringing profitability to the fast growing revenue trend of this industry.

THE IMPORTANCE OF PLANT AND PROCESS DESIGN
Plant and process design is important in most industries; however, this is particularly the case in the biotech industry. Building a biotech plant may take up to eight years and cost several billion pounds. A change in an existing plant or a process may be very expensive and time-consuming. In fact, the FDA may even require companies to re-do clinical trials following changes in existing processes. Therefore, decisions concerning investments in new facilities or expansion plans and competing biotech technology (for example, continuous perfusion versus batch) have an impact on the long-term profitability of the company. Companies need to make sure that these decisions will meet the requirements of unknown, long-term outcomes.

Biotech companies today employ large process engineering groups whose focus is to analyse and optimise manufacturing processes. Most process engineers use simulation tools that enable them to develop models for mass energy balances, estimating waste and peak and average utility consumption and so on. While these simulation tools enable engineers to precisely model chemical and biological processes, they lack the sophisticated optimisation capabilities necessary to provide a holistic view of the manufacturing processes and generate realistic plans and schedules taking into account all manufacturing constraints. Using simulation tools, engineers are able to simulate the dynamics of a single batch in an empty plant, but they are unable to simulate the intricacies and dynamics of several batches running in the same facility and using shared equipment, support operations and utilities.

Today, the main goal of plant and process design is to find the right size of equipment and operating procedures for new facilities, expansion plans and process changes. In this context, scheduling of batches becomes more important than generating a very precise model of chemical and biological reactions.

An alternative is to use a tool such as the ILOG Plant PowerOps to simulate different plant configurations using a simple user interface. Designed for manufacturing planning and scheduling, it enables engineers to test different plant configurations against alternative future demand trends and find the right balance between cost and manufacturing capacity. It also enables them to discover hidden bottlenecks and make strategic decisions based on realistic simulations of manufacturing schedules.

The ability to use the same tool for plant design and for planning and scheduling production operations has additional advantages. It allows planners and engineers to work off the same data and make decisions based on the same manufacturing models.

CONCLUSION
Flexibility is central to ensuring that the pharmaceutical industry can cope with an increasingly complex and variable manufacturing environment. While statistical analysis can greatly help companies reduce variability, this alone is no longer enough. In order to ensure flexibility, companies need to improve their processes and operations, and optimisation is central to this. Consequently, it has become clear that integrated planning and scheduling tools are central to developing the manufacturing flexibility necessary to ensure competitiveness and success in today’s changing industry environment.

Reference