01

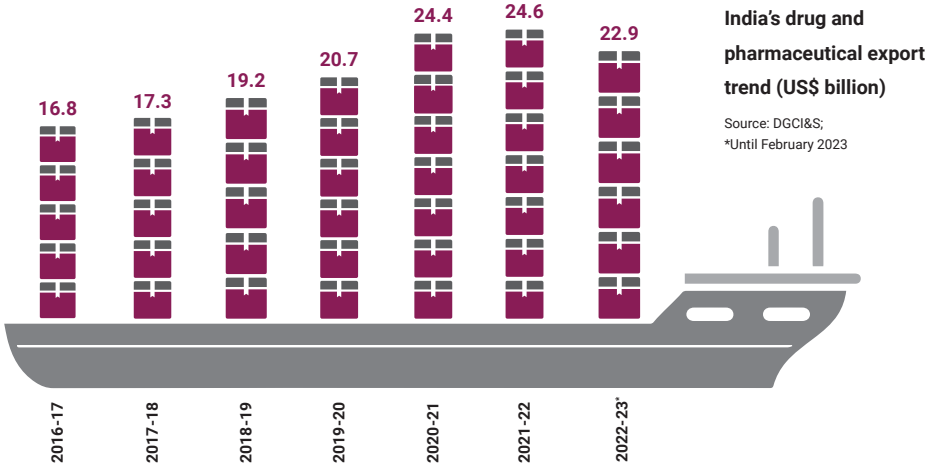
Accelerated Pharma Manufacturing

Authored by
Chandrachur Datta,
Dr. Shelja Jose Kuruvilla
& Achal Pande

Pharma manufacturing faces unique market and operational challenges. When an attempt is made to manage this high-uncertainty environment with the typical method of monthly production planning, it precipitates a vicious loop of issues. Only a dynamic approach that ensures flexibility on the shop floor can sustainably ensure reliability and high output.

INDUSTRY BACKGROUND

India is often described as the "pharmacy of the world". Exports from the country have been steadily growing over the years. During the year 2021- 22, the country exported pharma products worth US$ 24.62 billion even as there were global supply chain disruptions[i]. India's pharmaceutical exports this fiscal year are set to grow by 6.3% and hit sales of $27 billion, driven by strong US buying[1] .



India's drug and pharmaceutical export trend (US$ billion)

Source: DGCI&S;
*Until February 2023

However, all is not rosy. The pharma industry has been facing a chronic conflict in the way operations and supply chain is managed that can threaten long-term growth and profitability in the industry. Demand variations from the US and other global markets are increasing. This is not only due to causes such as surges in consumption (e.g., a pandemic - outbreak of Malaria or Diarrhea), seasonality (e.g., more antibiotics are sold at the onset of winter), changes in regulatory guidelines (e.g., banning of a certain substance), etc., but also due to supply disruptions from other manufacturers. To respond quickly to this unpredictable demand, companies want to be more agile in operations.

Notes

Industry Conflict

However, agility is difficult for companies to build into their processes. This is because operations in pharma companies, are very rigid and enjoy very little flexibility by necessity - due to the stringent quality norms set by regulatory authorities. For instance, the route or fixed set of machines specified in the Batch Manufacturing Report (BMR) specifies a fixed set of machines or the route through which a batch of a particular drug has to be processed cannot be changed. There is also systematic and rigorous testing to be done at various stages that cannot be subverted or compromised.

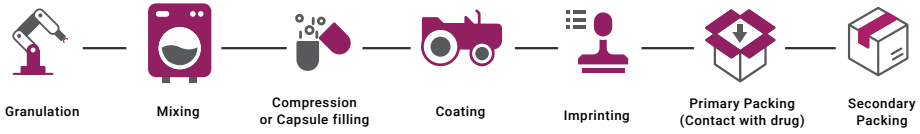
Moreover, most generic pharma businesses face challenges to their profitability when competition intensifies, and there is consequent price erosion. Recently, the US market (the largest generic market) has seen mega consolidation deals involving large distributors. This emergence of a few large pharmacies that control 85% of the US market has resulted in further pricing pressure for many companies. The pursuit of agility and flexibility in this environment might endanger the much-needed costefficiency and undermine the long-term sustainability of firms.

Notes

Raw Material (RM) or Packaging Material (PM), after they are received from suppliers (located in different parts of the globe), go through a pre-designed, elaborate testing process with very stringent sampling requirements – 100% sampling is done for every shipment. The quality approval may take anywhere between six to 15 days (There are microbiological processes for which the testing time itself is six days). This is important because any variation in the quality of raw material – whether in the chemical starting material or in the glass vials for final product packaging – can have a direct impact on product yields, costs, regulatory submissions required, bio-availability, and most importantly, patient safety.

Rigid production routes

The basic capsule/ tablet making process is as given below:



The manufacturing process (especially for products meant for highly regulated countries such as the USA) is pre-documented, including details such as the size of a single batch, raw material details and quantity, the machines used for processing, processing time, etc. This document is called a Batch Manufacturing Report (BMR). **The BMR specifies a fixed set of machines (Granulation 3 -> Mixing 5 -> Compression 4 -> Packing 6) or the route through which a batch of a particular drug has to be processed.** The route may change if the batch size changes, even if it is the same drug. In other words, every batch progresses through the manufacturing facility in a pre-defined route. The possibility of changing the route is minimal. In fact, the whole factory can be described as a large congregation of many small factories dedicated to each product.

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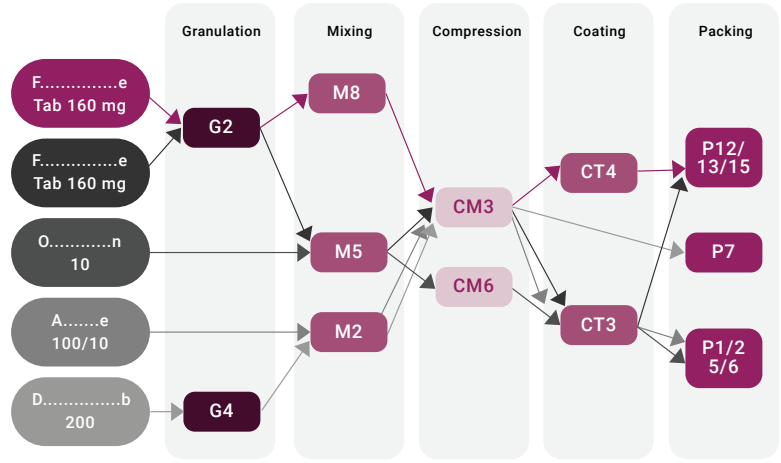


Illustration of pharmaceutical drug manufacturing routes

Elaborate Quality Control Process

There may be in-process testing after some or all stages. Any exceptions would be considered 'out-of-specification' or 'out-of-trend' (OOS/OOT) depending on extent of variation. This would require a thorough investigative process to unearth the root cause.

Complex Documentation Process

The actual parameters (temperature, pressure, speed of a machine, die used for testing, etc.) of various stages during the processing of a batch have to be observed and recorded for any future investigation. At every stage, there is a pre-approved (as per BMR) hold time. If this time is surpassed, it would warrant an investigation.

Notes

SOLUTION THAT DID NOT WORK

Operational Challenges

The monthly manufacturing plan is created that consists of campaigns, i.e. 3-10 batches, which have to be released and produced one after the other, formed by clubbing requirements/orders across months. Procumbent, QC and release/ dispensing are expected to align with this plan.

Challenges in procurement

To ensure timely availability of raw materials, procurement would place orders with vendors as per the sales forecast and provide a delivery schedule as per the monthly production plan. However, due to fluctuations in the availability of some raw materials or due to urgencies from the market, **often, the monthly plan has to be changed. Once the plan is changed, procurement would be under pressure to expedite any raw material necessary as per the new plan,** but which is currently out of stock. Since the lead time of certain raw materials is very high, these may have to be shipped by air at additional costs. But at the same time, the raw material already procured or in the pipeline would probably remain unutilized for months. The impact of this dysfunctional way of managing procurement shows up in the books of the company as excess inventory (leftovers of forecast changes), write-offs, and expediting costs.

~40%-50% of RM SKUs do not arrive on time in the required quantity

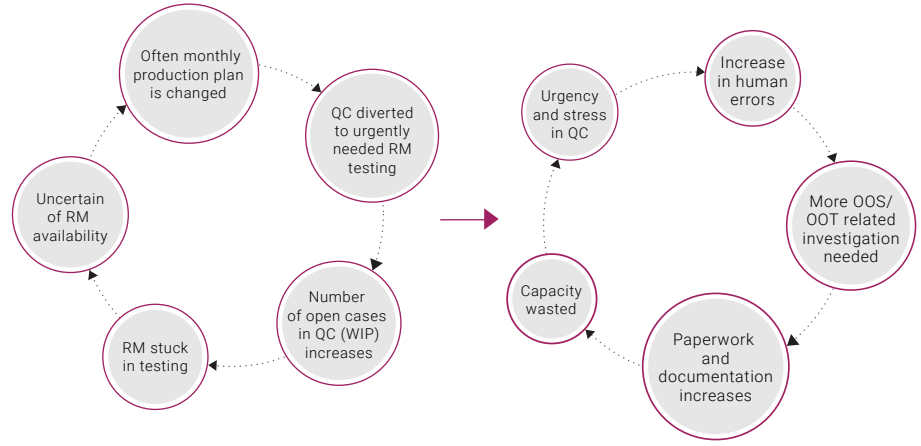
Firefighting and stress in QC

The change in the monthly plan also has an impact on QC. As discussed earlier, the quality checks in this industry are stringent and time-consuming. Thus, to ensure that the manufacturing processes go on unhindered, quality checks on all inputs for a release have to be completed upfront and kept ready. As the releases are planned for a month, the QC department also plans their raw material for the whole month. However, changes in the monthly plans essentially break campaigns and lead to unplanned consumption of raw materials. In these circumstances, QC capacity is diverted to complete testing as per the new plan. Often, changes are done at the last minute (towards the month-end). Consequently, there is urgency and stress in the QC department. With capacity diverted to unplanned testing, the number of open cases (WIP) tends to increase.

Notes

When WIP is high and 'what production is asking for today' is a priority, the availability of raw materials for subsequent orders becomes more uncertain.

This loop, which sets in due to a scramble to procure raw materials, becomes the cause of and feeds another vicious loop. In an environment of urgencies and frequently changing priorities, the chances of human error increases. And, in this highly regulated and prescribed environment, any 'Out-Of-Specification' (OOS) or 'Out-Of-Test' (OOT) automatically triggers a time-consuming investigation with the attendant paperwork. When capacity, which is already under pressure, is wasted on these tasks, it increases urgencies and stress in the department.



The vicious loops in quality control department

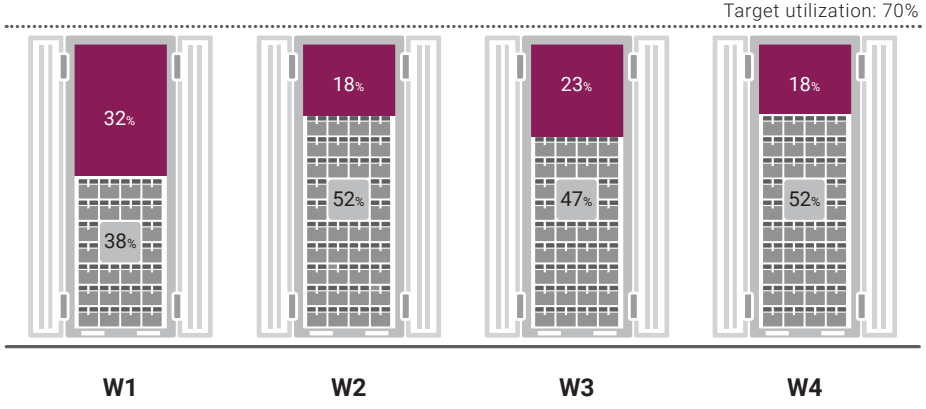
Overload and Underload of production routes

Once procurement and QC arrange for the necessary raw materials, the dispensing of batches is done as per the monthly plan. These starting departments process these batches without any issues. However, since every product has a fixed route, and these routes crisscross each other (much like the interconnected road network of a large city), at times, multiple batches of a campaign could arrive all together at some downstream department. Thus, **occasionally, some work centres might receive multiple orders, all waiting to be processed – an overload situation.** At times, some batches are processed faster than anticipated, or orders may be stuck upstream, which leads to an underload situation.

Notes

Lower output and poor On-Time In-Full (OTIF)

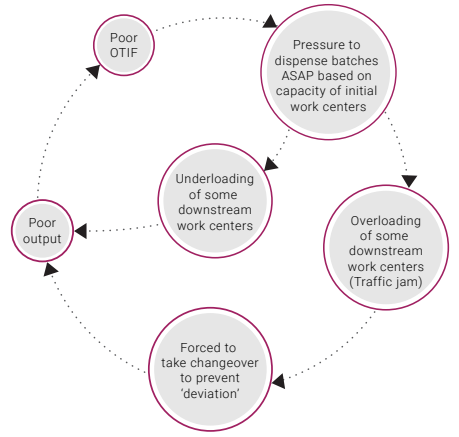
Dispensing of new batches or the campaign continues as per the monthly plan, irrespective of these emerging overload and underload conditions downstream, further aggravating the situation. The output of the empty/underloaded routes would naturally be low. The overloaded routes will also drop output eventually when they are forced to make unplanned changeovers to avoid potential 'deviations' arising from crossing hold time parameters. As outputs fall, the plant's on-time performance on orders falls too.



Snapshot of a month seen in a pharma plant showing 18-32% underutilized capacity (target utilization assumed @70%)

When a pharma manufacturing unit experiences repeated failures on OTIF, and plant managers face the wrath of irate customers, they inevitably feel the pressure to dispense orders to the shop floor as early as possible (in an attempt to finish sooner). **The more the plant dispenses batches, the worse are the traffic jams, and poorer is the output.**

Notes



The vicious loops in pharmaceutical manufacturing

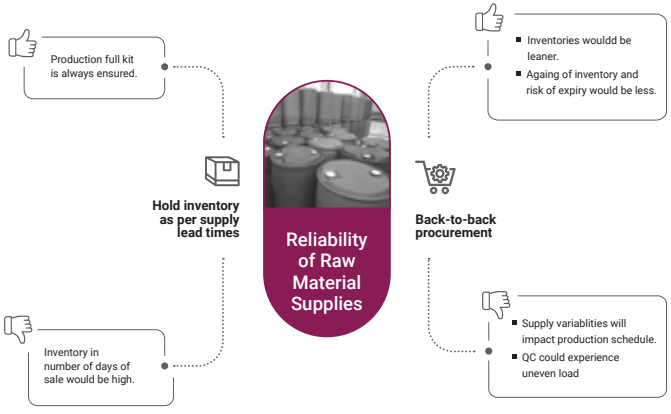
High FG inventory and High airfreight expenses

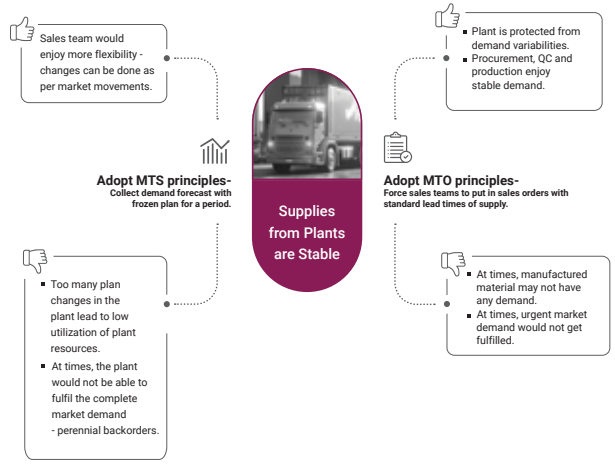
A low OTIF means that many orders run the risk of being delayed beyond the customers' tolerance. This is detrimental to the company in many ways. Delay in delivery of orders could lead to sales loss (there is usually more than one generic for a drug) and customer dissatisfaction. In certain countries, the companies could end up paying heavy penalties. This forces most companies to forecast demand on an aggressive side. But if demand does not pan out as expected, then companies have to deal with the problem of excess inventory in the warehouse. Consequently, **at any point in time, the warehouses may have as much as six to eight months of inventory for some SKUs!** To get rid of this additional inventory, the company either has to offer deep discounts or incinerate and write off the stock if it has passed its sell-by date.

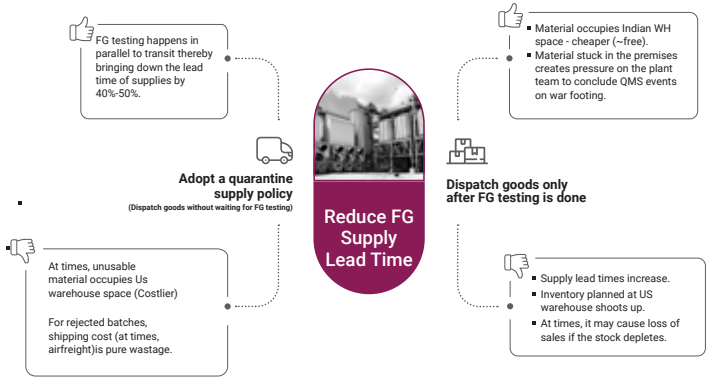
Moreover, every batch of drug manufactured has a clearly printed expiry date. Many countries have strict guidelines as to how much residual time should be available for the medicines when a batch reaches their port of entry. Further, the distribution channel will be very reluctant to accept stock nearing expiry since customers will not buy drugs nearing expiry. So, if the manufacturing of a batch is delayed beyond a certain point, then to ensure that it is not sent back from the port of entry and to meet customer expectations, the manufacturer is forced to send the shipment by air, resulting in additional expenses.Frequent instances of discounts, air freight, and write-offs can put a significant dent in the bottom-line.

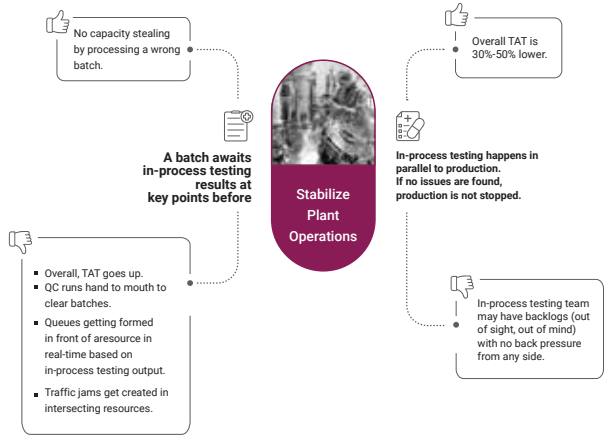
Notes

While companies often work as described above, there are other ways too in which companies try to achieve their objective of stabilizing plant operations. However, while each of these have their pros, they have their cons as well.







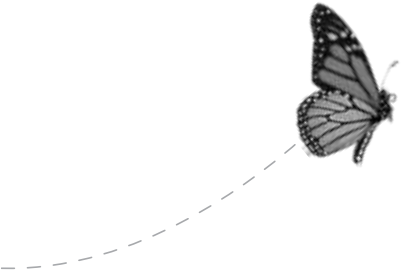


Note: Depending on the actions taken by companies in operations, there could be various combinations of the above scenarios possible.

Notes

Need to Challenge the Status Quo

Most pharma organizations have learnt to live with these challenges because many others in their industry follow similar practices and suffer from the same problems. Moreover, the fairly healthy gross margins this industry enjoys means that when forecasts are reasonably accurate, they make a windfall, and even when it is not as accurate, the business remains viable. However, **with increasing competition, complexity, velocity and volatility of markets, there is a realization that no forecast or monthly plan is going to be good enough to respond to market and business environment changes.** Moreover, such fragile supply chains can be derailed by black swan events, such as a pandemic. Continuing with the status quo can only lead to stressed supply chains, erosion of margins, and lowering of returns.



Notes

DIRECTION OF SOLUTION

The key paradigm shift required to improve both reliability and output simultaneously in this environment is to opt for a more dynamic approach to manufacturing, one which does not need to depend on sales forecasts or monthly planning. This approach not only affords greater visibility of the cascading impact of changes anywhere in the supply chain but also equips the pharma manufacturing plant to respond to these with agility.

The Solution

To enable the necessary flexibility in planning and on the shop floor, first, the support departments have to be decoupled from the vagaries in manufacturing.

Decoupling Purchase

Purchasing RM/PM should not be linked to each sales order. Instead, to ensure the daily availability of all RM/PM, the inventory level (norm) for each item that the company should be carrying at any given point in time should be defined. This inventory level should account for the confirmed sales orders that need the material, the safety stock required for the item, and the demand indicated in the latest Annual Operating Plan (AOP).

Notes

The norm for each item has to be then compared to the stock at hand every day, and priority should be assigned based on the chances of an item becoming 'stock out'. The purchase team can place orders and expedite shipments based on this priority. If this exercise is done daily, it can ensure that changes made in the sales orders/AOP will be immediately captured in it.

Decoupling Quality Control

A similar tactic can be implemented at RM-QC to ensure availability of QC-cleared RM. One can define the RM-QC cleared inventory level (norm) for each item that should be available at any given point in time, modified frequently to synchronize with the current manufacturing plan. This would be adequate to ensure seamless dispensing as per priority. For instance, it can be decided that the RM-QC team will enable 100% availability of all full kits for a two-week horizon and 80% availability for the forthcoming two weeks (total four-week horizon). This will decouple QC from the everyday urgencies of manufacturing.

Ensuring flexibility on the shop floor by aligning full kits for orders

Decoupling of purchase and QC will enable the availability of QC cleared RM/PM, but flexibility on the shop floor is only assured when there is a bank of full kits for orders in the immediate horizon perpetually ready. In addition to QC approved APIs, excipients and the packing materials in adequate quantities, a full kit implies all items, including documentation (BMR), approvals (customer sanctions, if any), required to produce a complete shipment at the pharma manufacturing plant. **A separate full kit team has to continuously work on creating these full kits so that the shop floor at no point has to wait for any item required as per the priority in manufacturing.**

Managing priority in pharma drug manufacturing

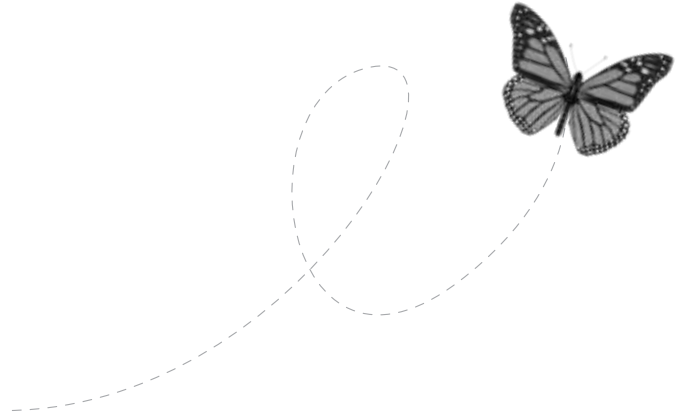
To synchronize the actions in manufacturing, it is necessary to create a simple yet unified system-driven signalling mechanism for priority, which can ensure that the on-time performance of customer orders is not jeopardised. For this, each order can be given a colour priority based on relative closeness to the due date. Red is the highest priority, then yellow, and green the least. Only this colour priority should dictate expediting at all workstations (no manual intervention).

Notes

Dispensing based on route load (WIP control)

The availability of full kits can free the shop floor from having to change plans due to fluctuations in RM availability, etc. Nevertheless, even now, dispensing based on monthly plans can clearly lead to development of bottlenecks and the starving of some resources downstream. This can be avoided if forming large campaigns by clubbing orders in advance is discontinued, and dispensing is done dynamically (possible due to full kit availability) based on the load of the entire route on a given day.

As the first step, all different possible routes in the factory are mapped, and the optimum load on each is determined. For example, let us say there is a route: Granulation 3 -> Mixing 5 -> Compression 4 -> Packing 6, and the optimum load on this route is 15 days. Every day, the planning team should evaluate the route load in the pharma manufacturing plant by taking into account the dispensed WIP batches. On any day, if the route load is more than optimum (>15 in the example), it is designated as overloaded, and dispensing in that route is stopped. **Dispensing will only happen for routes where the load is less (<15 in the example) and to the extent of the difference.** Dispensing will always be in adherence to priorities. However, if there are routes that are underloaded, the planners can pull future orders to be dispensed ahead of their planned time; but this is not allowed on overloaded routes.



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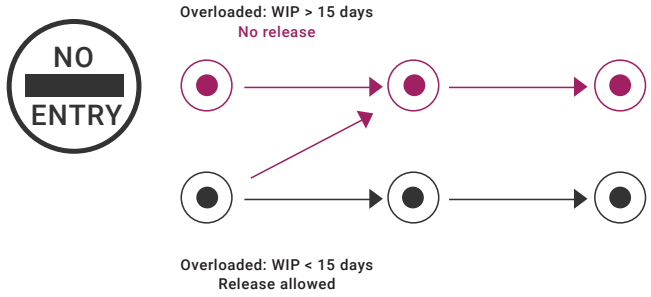


Figure 5: Illustration of how overloaded and underloaded routes (both with WIP limit = 15 days) are treated in dispensign

The source of capacity relief in pharma manufacturing plants

The availability of full kits well in advance will ensure:

- Flexibility to do daily planning based on route load in dispensing
- Pull ahead of future orders for underloaded routes without expediting in feeding departments
- Smooth flow of orders through the production process. For example, now the routes will not get choked with orders waiting for packaging material

The tactic of dispensing based on route load and clear priority enables:

- Improved flow and synchronization of orders for overloaded routes
  Increased output owing to reduction or removal of capacity wastage due to
- unplanned changeovers and other unplanned documentations
  Better utilization of the underloaded routes - Increases Output

Capacity improvement initiatives

When route loads are evaluated, if it is seen that a few routes are continuously overloaded, this signals the existence of real constraints in the system. These routes have to be studied, constrained work centres identified, prioritized, and actions taken to improve their capacity. Taking up such focused capacity improvement initiatives on the specific work centres helps in improving the flow and increases the system output further.

Notes

CONCLUSION/RESULTS

The demand for drugs will go up in the wake of a pandemic. The world will look to the pharma companies to meet this demand. To rise to this challenge, these companies have to redesign their operations to be more effective, identify hidden capacity, and be more agile. The above **steps enabling flow of orders will not only align all the processes and departments, but also reduce lead time, and increase the output of the pharma manufacturing plants.**

This will enable companies to respond speedily to variations in demand, thereby positioning them at the forefront of the fight against any pandemic.

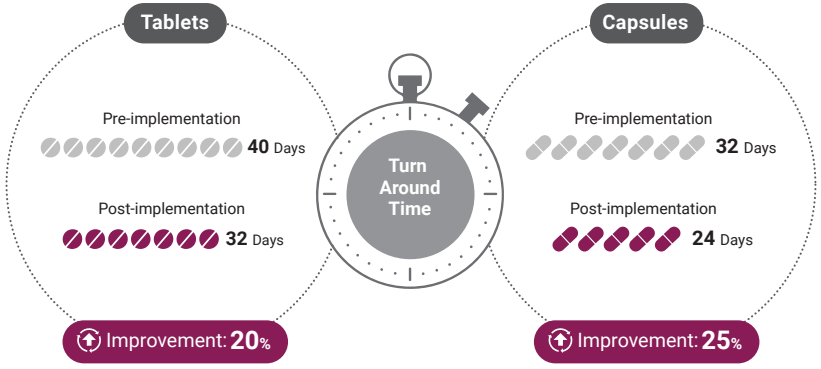
CASE STUDY

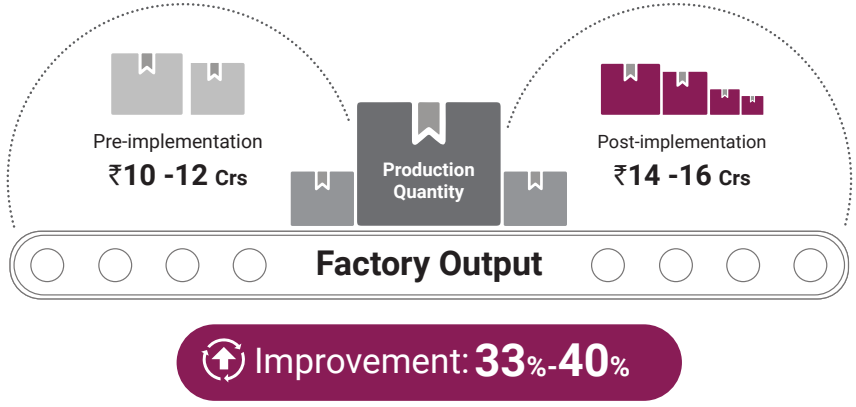
One of India's leading pharmaceutical exporters decided to opt for this dynamic approach to manufacturing, which responds daily to emergent machine loads. They also decoupled the procurement and quality teams so that they, protected from the vagaries in manufacturing, can ensure continuous availability of full kits as per the priority in manufacturing. With this new approach and by enabling auto replenishment of RM/PM, the company experienced better synchronization of full kit for dispensing both from procurement and QC, timely visibility of any shortages, better synchronization in FG QA stage for BMR (Batch Manufacturing Record), BPR (Batch Packing Record) & QMS activities, and elimination of stress across all functions in the plant.

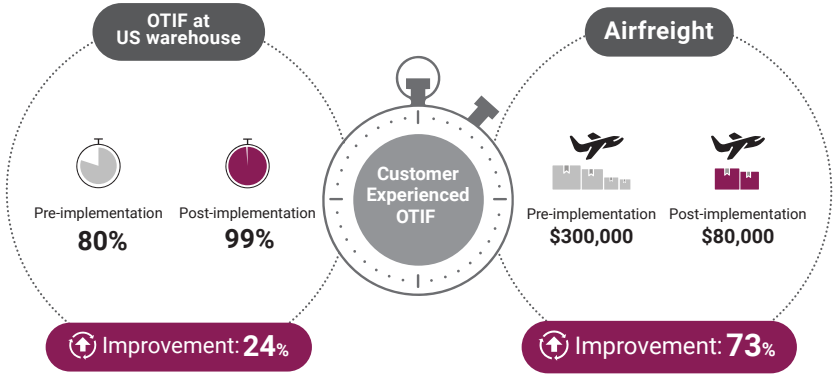
The crashing of lead times by one-third and the ability to track orders on a day-to-day basis also makes managing demand easier for marketing and other stakeholders.

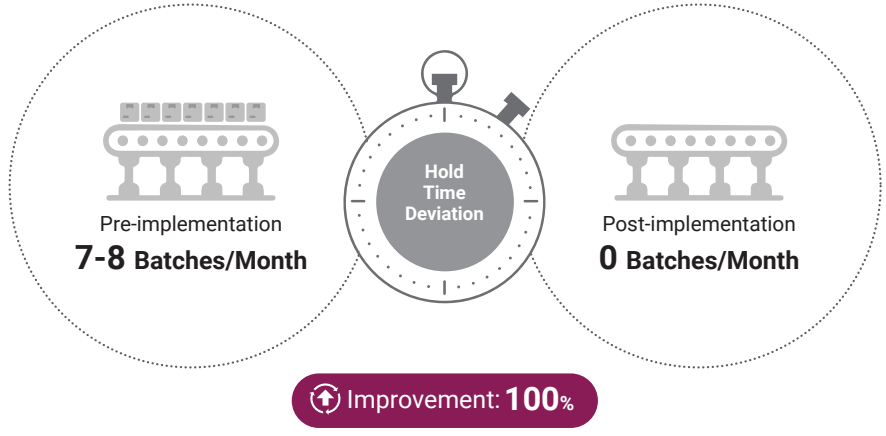
Notes

Some of the salient results of implementing the new dynamic approach to pharma operations are shown below:









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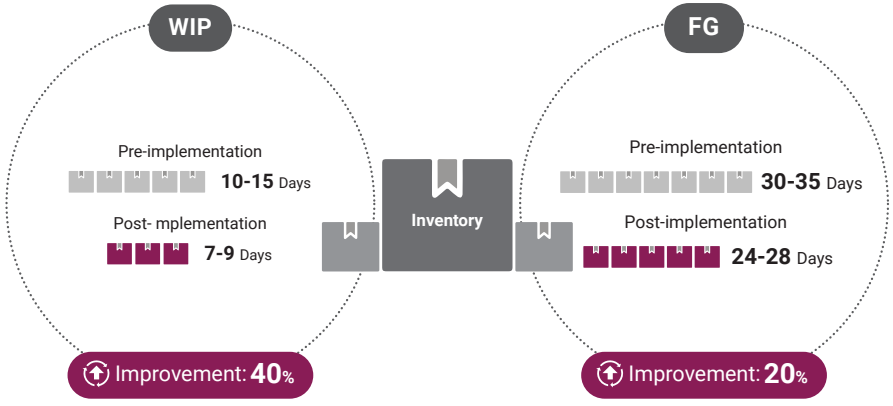
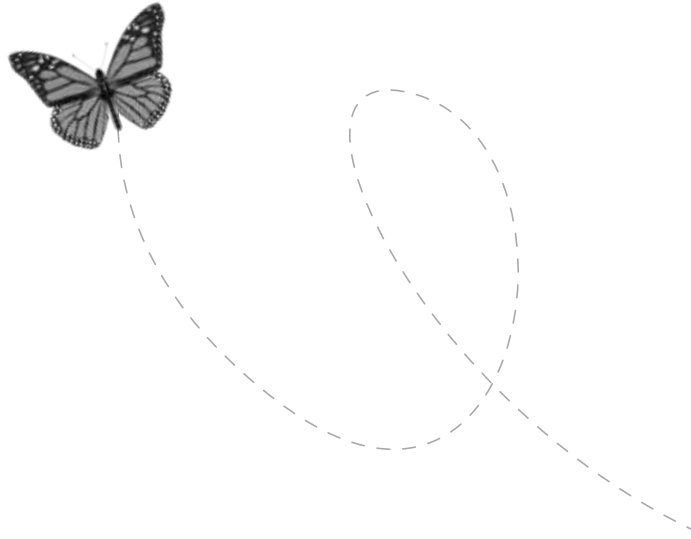

WIP
Pre-implementation
10-15 Days
Post- mplementation
7-9 Days
Improvement: 40%
Inventory
FG
Pre-implementation
30-35 Days
Post-implementation
24-28 Days
Improvement: 20%



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