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DE-STRESS TO DELIVER

Accelerated pharma manufacturing

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The outbreak and spread of the novel coronavirus has led to a dramatic surge in global demand for pharmaceuticals. As India is one of the top global drug suppliers of generics, it is being approached with sizable orders by many countries including US, Australia, Brazil, and several South Asian countries. To meet the rising wave of both domestic and export demand, Indian pharma plants will have to ramp up capacity and increase output from existing capacity. This, however, is not simple for these companies. There are many challenges endemic to this industry which makes this an uphill task.

Industry challenges

Variability in demand

Demand in pharma markets is determined by a complex combination of factors. It can vary based on surges in consumption (e.g. the ongoing pandemic/outbreak of malaria/diarrhoea), seasonality(e.g. more antibiotics sell at onset of winter), non-supply from a competitor, change in regulatory guidelines (e.g. banning of a certain substance) etc. Many of these factors are very difficult to predict and plan for in advance. However, since supply lead times are characteristically high in this industry, all manufacturing companies have to forecast approximately three to six months consumption. This then forms the basis of sales and operations plans of firms. This process becomes more complicated when companies are trying to deal with demand patterns of different global regions and nations with different regulatory frameworks.

Supply to multiple and strict regulatory frameworks

Manufacturing medicines is a serious business – even the quintessential paracetamol might cause deadly infections or complications if the dosages are not right or if there is presence of contamination. Therefore, there are regulatory bodies in every country like the Food & Drug Administration (FDA) in the USA and their often extensive and ever changing regulatory requirements that pharmaceutical companies have to comply with, to be able to sell in those respective countries. These requirements determine the quality standards and guidelines not only for the manufacturing process but also for procurement of materials transportation, storage, and distribution of medicines (drugs).

Stringent quality standards

Every drug has two major categories of raw material components:

- **Active pharma ingredients or APIs** – The core chemical component or the biologically active component in a drug product which treats an illness or condition.
- **Excipients** – Inactive substances that serve as the vehicle for the drug. E.g. substances that bind/coat APIs to form the tablet or capsules.

In addition to these, another crucial input is packing material. Primary packaging is that which comes in direct contact with the drug – e.g. bottles, foils etc., secondary packing materials are those which constitute the external packaging – e.g. paper or cardboard boxes.

Raw material or packaging material, after they are received from suppliers (located at 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 chemical starting material or 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 include these processes:

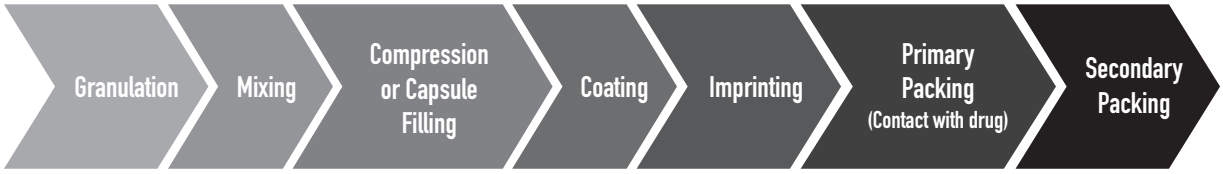

Figure 1 : Capsule/tablet making processes

The manufacturing process (especially for products meant for highly regulated countries like 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. If the batch size changes, even if it is the same drug, the route may change. In other words, every batch progresses through the manufacturing facility in a predefined route. Once dispensed to the shop floor, 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 for each product.

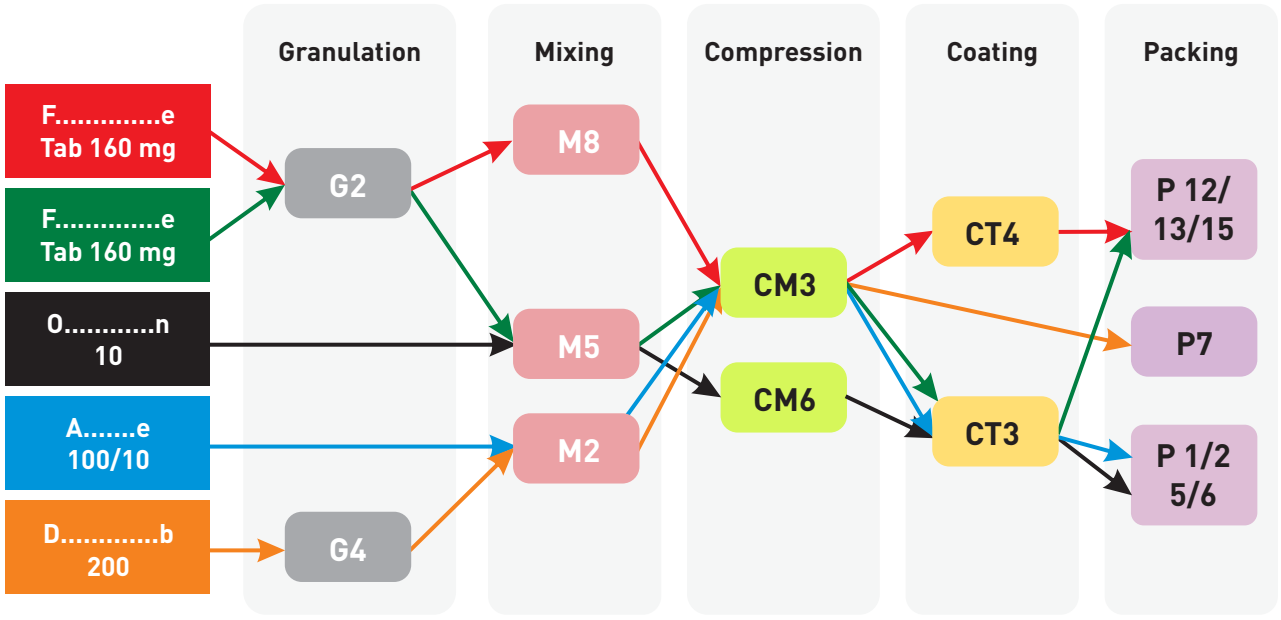

Figure 2 : Illustration of drug manufacturing routes

Complex and detailed checking and 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. And after every stage, there is quality testing. Any exceptions would be considered "out-of-specification" or "out-of-trend" (OOS/OOT)". This would again require a thorough investigative process to unearth the root cause. Any deviation from BMR has to be approved. And all such approvals, deviations, investigations have to follow a predesigned process and have designated signatories. Consequently, there is a lot of paperwork, multiple to-and-fros between manufacturing, plant QC, plant QA, central QC, and central QA teams, all generating additional tasks for the manufacturing workforce.

Elaborate changeovers (set-ups)

Each step of the process can be complex. The manufacturing facility is a highly secure one with separate air circulation, air pressure, and temperature controlled chambers for each machine. For example, if the granulation process has six machines of different capacities, they will be placed in six separate chambers with no contact whatsoever between them. These chambers are thoroughly cleaned as part of the changeover process (between two different formulations) to avoid contamination. Every changeover is signed off by Quality Control (QC) and Quality Assurance (QA) teams to give go-ahead for production. The changeover process is significant even in the case of change of dosage for the same drug. Such an elaborate process of changeover takes considerable time – as much as 30% to 40% of the available machine hours.

Operational Challenges

In this complex environment, manufacturing small batches in frequent intervals is seen as leading to capacity wastage. So, a monthly manufacturing plan is created which 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 is expected to align to this plan.

Challenges in procurement

In order to ensure timely availability of RM, 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 RM necessary as per 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 RM already procured or in the pipeline would probably remain unutilized for months. Once they age beyond their usable period, the company has no choice but to incinerate it. 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.

Firefighting and stress in QC

The change in 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

goes 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, QC also plans RM for the whole month. However, change in the monthly plans essentially breaks campaigns and leads to unplanned consumption of RM. In these circumstances, QC capacity is diverted to complete testing as per the new plan. Often, changes are done at the last minute (towards month end). Consequently, there is urgency and stress in the QC department. With capacity diverted to unplanned testing, number of open cases (WIP) tends to increase. When WIP is high and 'what production is asking for today' is priority, availability of RM for subsequent orders becomes more uncertain.

This loop which sets in due to expediting for RM, 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" or "out-of-test" 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.

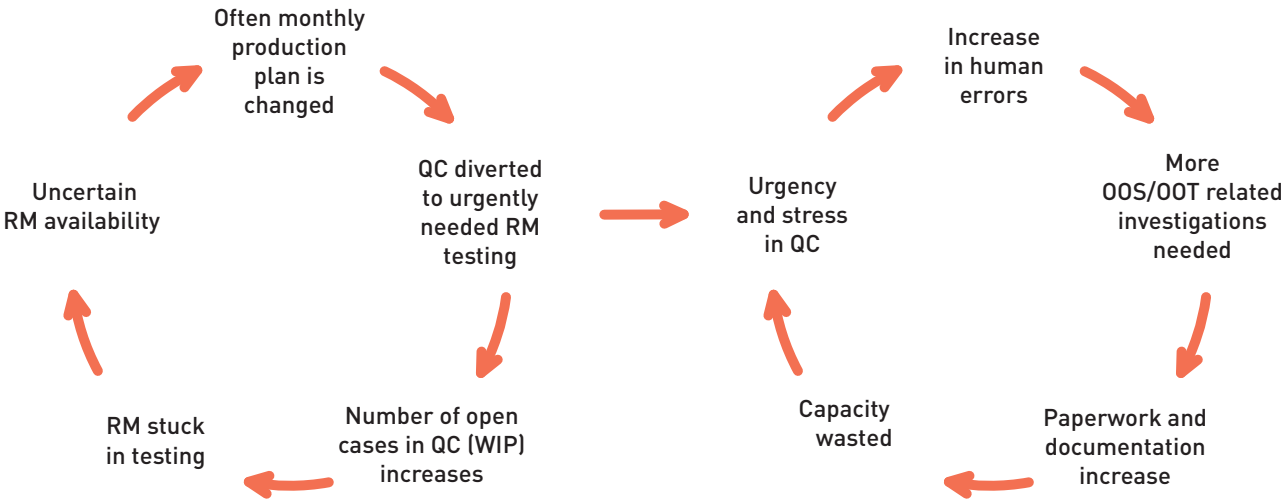

Figure 3 : The vicious loops in quality control department

Overload and underload of routes

Once procurement and QC arrange for the necessary RM, the dispensing of batches is done as per the monthly plan based on available capacity of the initial departments. These starting departments process these batches without any issue. 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, from time to time, some work centers might receive multiple orders, all waiting to be processed – an overload situation.

At times, some batches are processed faster than anticipated, and that would lead to clearing of some routes. In the absence of anything else in the monthly plan for these machines to process, these routes would continue to remain empty –an underload situation.

Lower output and poor 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 output fall, the plants' on-time performance on orders fall too.

When a plant experiences repeated failures on OTIF and plant managers face the wrath of irate customers, they would 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, worse are the traffic jams, and poorer is the output.

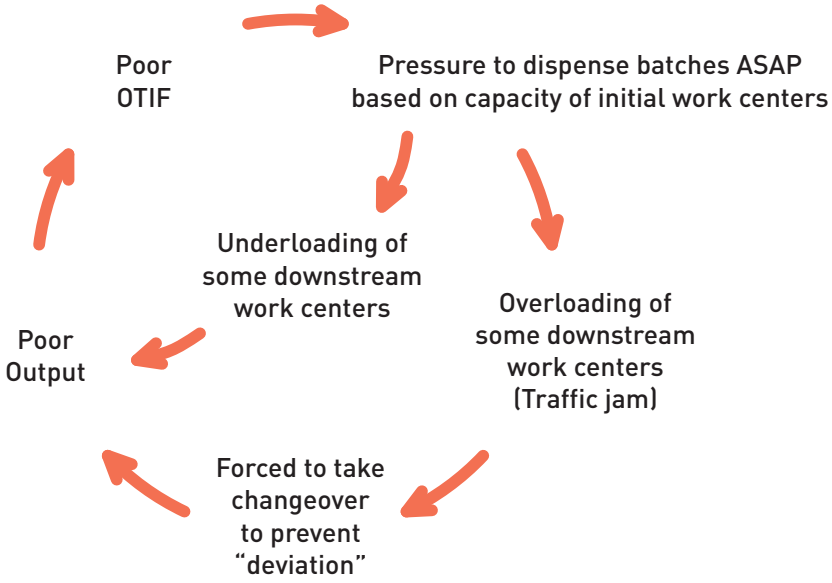

Figure 4 : The vicious loop in pharmaceutical manufacturing

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 of 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.

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's 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 like the current pandemic. Continuing with status-quo can only lead to stressed supply chains, eroding of margins and lowering of returns.

Direction of solution

The key paradigm shift required to improve reliability and output 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 manufacturing plant to respond to these which 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 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, a safety stock required for the item, and the demand indicated in the latest annual operating plan (AOP).

The norm for each item has to be then compared to the stock at hand every day, and priority should be assigned based on chances of an item becoming 'stock out'. Purchase team can place orders and expedite shipments based on this priority. Doing this exercise daily, can ensure that any changes made in the sales orders/AOP would 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 an 80% availability for the forthcoming two weeks (total four-week horizon). This will decouple QC from everyday urgencies of manufacturing.

Ensuring flexibility on the shop floor by aligning order full-kit

Decoupling of purchase and QC will enable 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 and excipients, and the packing materials in adequate quantities, a full kit implies all items including documentations (BMR), approvals (customer sanctions, if any), required to manufacture a complete shipment at the 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 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 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 highest priority, then yellow, and green the least. Only this colour priority should dictate expediting at all work stations (no manual intervention).

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 plan can clearly lead to developing of bottlenecks and 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 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's 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 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's 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 but if there are routes which are underloaded, the planners can pull ahead future orders to dispense but this is not allowed on overloaded routes.

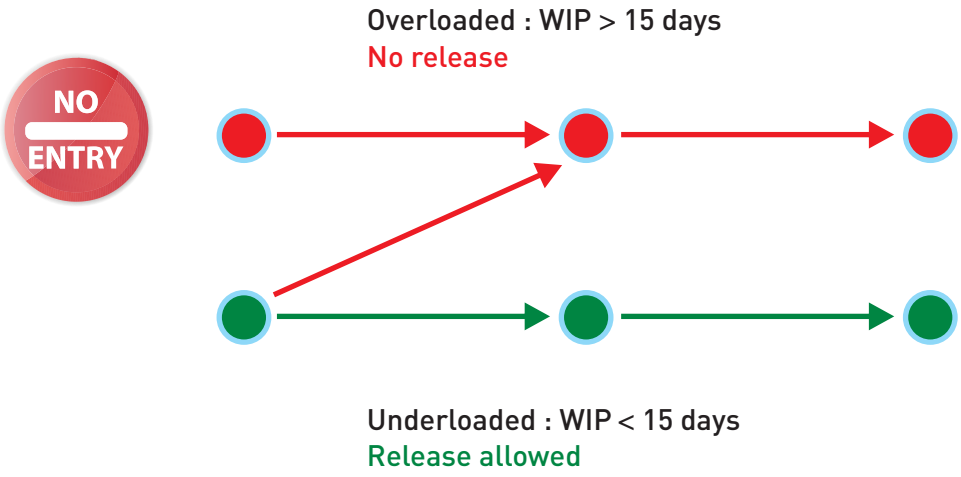

Figure 5 : Illustration of how overloaded and underloaded routes (both with WIP limit = 15 days) are treated in dispensing

The source of capacity relief in plants

Availability of full-kits well in advance will ensure:

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

Tactic of dispensing based on route load and clear priority enables:

1. Overloaded routes will experience improved flow and synchronization of orders
2. No wastage of capacity due to unplanned changeovers and other unplanned documentations. Increases output.
3. 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 focussed capacity improvement initiatives on the specific work centres helps in improving the flow and increases the system output further.

Conclusion

The demand for drugs will go up in the wake of the pandemic sweeping across the globe. The world is looking 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 output of the plants. This will enable companies to respond speedily to variations in demand, thereby positioning them at the forefront of the fight against the pandemic.