Supply and Demand

A trial's success is seldom attributed to the supply chain yet, through a closer collaboration between clinical operations and clinical trial supply teams, it may be possible to deliver them more effectively and efficiently

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The R&D of a new molecular entity (NME) is a constant battle and requires trade-offs between the budget set by the organisation, product development goals, personnel available and the public health issues of the country. The total worldwide R&D expenditure of pharmaceutical and biotechnology companies increased from $108 billion in 2006 to $141 billion in 2015 (1). Paul *et al* reported that:

- Drug discovery and preclinical development account for 33% of the total cost per NME ($281 million)
- Clinical development (Phase 1 to submission) represents 63% ($548 million)
- Submission to launch costs 5% of the overall expenditures per NME ($44 million)

Discovery research lasts four and a half years; preclinical testing continues for a further year; the three clinical development phases take 1.5, 2.5 and 2.5 years respectively; and the phase from submission to launch requires another 18 months (1). The above is a clear testimonial of the significance of the whole clinical research process that accounts for the majority of the cost and time involved in bringing an innovation to market.

Clinical operations (CO) is the backbone of the entire research process. It is through flawless trial design, execution and oversight that NME's can seamlessly enter the market. But can CO alone enable a drug's smooth entrance?

Overlooking CTS: A Serious Oversight

The constant upheaval in regulations with respect to clinical trials involving human volunteers in every corner of the world has mandated each aspect of a study to be tightly scrutinised and controlled. By virtue of this, the role of project management has escalated to a much higher pedestal, with the expectation that better planning and forecasting will lead to optimum time and resource utilisation.

There is a need for increased awareness of the contributions of the supply chain in the success of a trial, and the involvement of complex and expensive investigational supplies. In many cases, key operational assumptions such as packaging material, delivery method, site selection and supply chain documentation made while designing a study protocol all lack input from the clinical trial supply (CTS) team, leading to several road blocks at the execution stage and severely hampering project timelines.

Overlooking the greater role played by CTS teams – not just during execution but even conceptualisation – is a serious oversight that has given rise to an urgent need for better linkages between the CO and CTS staff to conjure the most viable investigational product (IP) management plans. This close synergy offers a number of advantages to the health of a trial, some of which are as follows:

Getting the Product Packaging Right
Conventionally, it is the sponsor who assumes the upper hand in product packaging and distribution. However, from a trial point of view, CO and CTS teams can provide several practical inputs that can go a long way in efficient IP management.

A study participant's compliance with treatment regimen is critical – poor adherence can jeopardise the data collected. As such, packaging and labelling techniques should be finalised only after careful evaluation of the study design by both CO and CTS teams. Practical inputs from these teams towards product design – such as easy-to-open bottles, blisters and daily dispensers for the geriatric demographic,

attractive packaging for participants of a younger age group, and easy to carry, on-the-go medications for the working class – have gone a long way in increasing compliance.

Another important aspect that requires the strategic guidance of both teams is IP-material interactions. The packaging should be inert in nature so that it does not affect the IP's quality and strength. To pre-empt this, input must be sought from experts and can be facilitated by the CTS team. For example, while using a glass vial for packaging, one has to take into account the leeching of metal ions that could cause metal ion toxicity or hasten drug degradation. To avoid any surprises during the course of a trial, it is essential for the CTS vendor to be proactively involved during the design stage.

Labelling also plays a major role in controlling costs and enhancing subject compliance. Labels need to not only meet regulatory requirements, but should also give clear and sufficient information to participants regarding drug administration and storage conditions. The CO and CTS teams can decide the right type of label – such as single panel and booklet – depending on the nature of the IP, its package design, storage conditions, whether the study is single- or multi-country and so forth.

In blinded trials, packaging plays a crucial role in randomisation and maintaining blinds. Studies involving reference products face an additional challenge of masking the identity of the marketed or non-marketed reference product and ensuring that both drugs are indistinguishable to the blinded group.

For instance, in vaccine trials involving a marketed reference product and an IP that only differ in physical appearance, challenges arise in maintaining appropriate blinding. Since the primary product design cannot be altered, it is now up to the CO and CTS teams to develop a suitable secondary product design. Both teams need to deliberate and create an appropriate blind such as a sticker label that completely covers the vial and syringe, thus eliminating the risk of a visual breach. The CO team would be responsible for ensuring that the secondary label meets all local regulatory requirements, while the CTS team must decide on appropriate material for the label that will withstand the conditions of storage and handling.

The Right Product at the Right Place at the Right Time

Accurate site selection has always topped the list of must-dos for successful study execution. While enough is being done to ensure investigator qualification and site infrastructure, choosing site locations is proving difficult. Regulations mandating equal geographic distribution of sites across a country or continent, the unavailability of already trained locations to take up more trials due to paucity of time and/or staff and high financial expectations of experienced sites have forced the CO team to search the far corners of the globe. This can often lead to challenges in seamless logistics, ultimately breaking the supply chain.

Timely involvement of the CTS team can help discover early solutions, avoiding last-minute problem solving.

They must rightly identify the best and fastest routes to reach them, factoring in possible delays due to weather and poor connectivity and thus enabling better execution of studies at such locations.

Multi-country trials tend to be complex and require appropriate conceptualisation of study execution. Both CO and CTS teams must address challenges such as IP packaging and licensing regulations, setting up a temperature-controlled supply chain as well as the management of returns and destruction – all of which must be customised for each participating country.

One potential solution is the appointment of local depots in participating countries. These should be GxP-compliant and provide an end-to-end service from receipt to the destruction of the IP. This poses a number of benefits such as:

- Shorter transit time to sites in that country
- Adequate knowledge of local regulatory requirements
- Availability of dedicated resources and project team handling ensuring timely action and customer focus

Drug Accountability

The FDA has listed drug accountability as 3rd in a list of top 5 findings during inspections. Reinforcing this, an FDA inspector went on to state that any individual should be able to perform drug reconciliation at an investigative site within 20 minutes.

The tractability of IPs from depots to assigned CTS facilities and respective sites and patients is the crux of the execution of a trial, and documentation is the only tool for auditors to track this. However, piling costs of conducting trials has forced sponsors to migrate towards targeted- and risk-based monitoring, leading to an appreciable reduction in expenditure and time without adversely affecting the quality of data. However, this has impacted drug accountability. With fewer on-site visits, the monitor is forced to complete large volumes of drug within limited monitoring visits.

In order to aid accountability and avoid integrity issues at the data submission level, there is a need for better planning at every step of the supply chain along with easy and effective documentation. It is often noted that, in studies involving a marketed drug, project management teams often ignore unique IP identifiers like kit and medication numbers since the product is marketed and may be purchased by subjects directly, against reimbursement. However, this could result in gross errors in drug return and accountability as the patient is less motivated to retain and return the used supplies to the site.

In such cases, the collaborative experience of both functions suggests routing of the IP via a centralised or local depot to maintain control over drug dispensing at each site. The long-term benefits of this added effort have been seen to overcome the cost implications of involving a depot, ultimately allowing for drug accountability to no longer be a hindrance in effective trial execution. An FDA inspector would love to see detailed tracking of the IP in a study right from the time of manufacturing, to storage in the depot, shipment to a site, administration to the right patient and return back to depot for final destruction. Coming together, an integrated plan involving the knowledge and expertise of the two teams can help

> “Some suppliers are responding by investing in strategies, in-house expertise and human and system resources to help biomanufacturers meet these needs, but others are not as responsive”

build a robust and leak-proof supply chain that will ensure the trial sails through inspection without any critical findings.

Another tool in aiding better accountability is the involvement of IP management systems. It is a myth that only randomised trials need this – with correct processes, all activities of drug management can be digitalised and automated. In fact, non-randomised trials benefit equally if not more. Project managers and CTS vendors are moving towards designing web-based solutions for all movements from the product's arrival at a facility through to its return and destruction. This helps with real time tracking of deviations and subject level compliance and practically eliminates situations wherein a site falls short of supplies (drug or ancillary). Also, given the fact that IP logs are the most incorrectly completed documents at site, such systems facilitate IP documentation by no small measure. The result is paperless but accurate and time-tracked documentation of IP movement.

Building Integrated Teams

Trials can no longer be conducted with sequestered teams. Today, greater association between all stakeholders of clinical research is the need of the hour and only with such partnerships can we expect the authenticity of generated data and overall quality of trials to reach greater heights. With the dynamic regulatory scenario, there is an increased need for translating the past experience of different teams for development of a well-thought out clinical trial design.

It is now time that we look beyond the traditional methods of designing, oversight and execution and work towards the development of one cohesive delivery function involving both CO and CTS teams as one cohesive excellence unit, with an unbroken chain of command and clear line of sight leading to optimum trial execution. By addressing the key challenges of trials and adopting emergent technologies, CO and CTS teams can achieve a future-proof supply chain that will positively address the changes within clinical research today.

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Reference

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