

# Stretched to the Limit

The shift towards global markets and the increase in specialised trials is putting the clinical supply chain under pressure. Successful management of outsourcing can improve this process at every stage.

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Most recent research on clinical trials focuses on outsourced R&D activities such as data delivery, site conduct and development. This article explores, for both sponsors and contractors, the clinical supply chain and manufacturing operations, from the manufacturing of active pharmaceutical ingredients (APIs) through to the delivery of investigational medicinal products (IMPs) at the clinical site and on to the patient.

Sponsors and contractors have undergone substantive change in recent years in response to the changing needs of the pharmaceutical industry. New technologies and target diseases lead to more complex and an increased number of trials and, in search of patient mass and lower cost, the clinical trial base has shifted towards markets such as India and China.

This has led to a drive for scale in some leading clinical research organisations (CROs) and the emergence of truly global players, while others have responded by focusing on emerging markets, adding niche and specialised services and targeting selected disease areas.

Many traditional activities have shifted to CROs, often with very different risk and reward mechanisms. The redrawing of the activity map requires new and more complex working practices involving multiple partners, often with differing motivations, and a consequent need to ensure that control is demonstrably sustained throughout the supply chain.

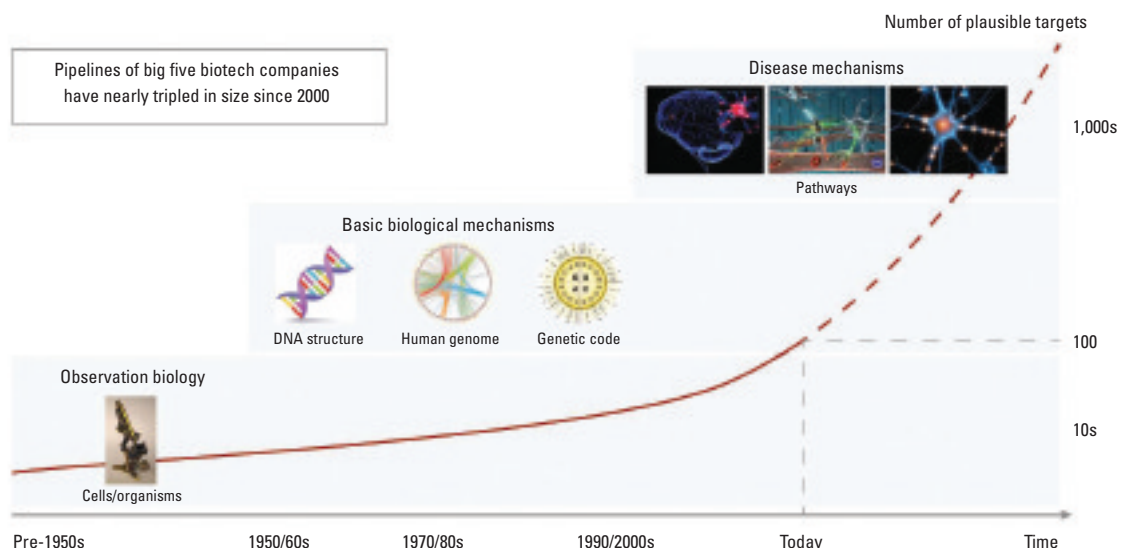
This puts increased demands on the CRO at a time when their finances are already under pressure, and the benefits are yet

to be realised. Sponsors remain, however, accountable for their clinical trials and therefore also need also to rethink and/or streamline.

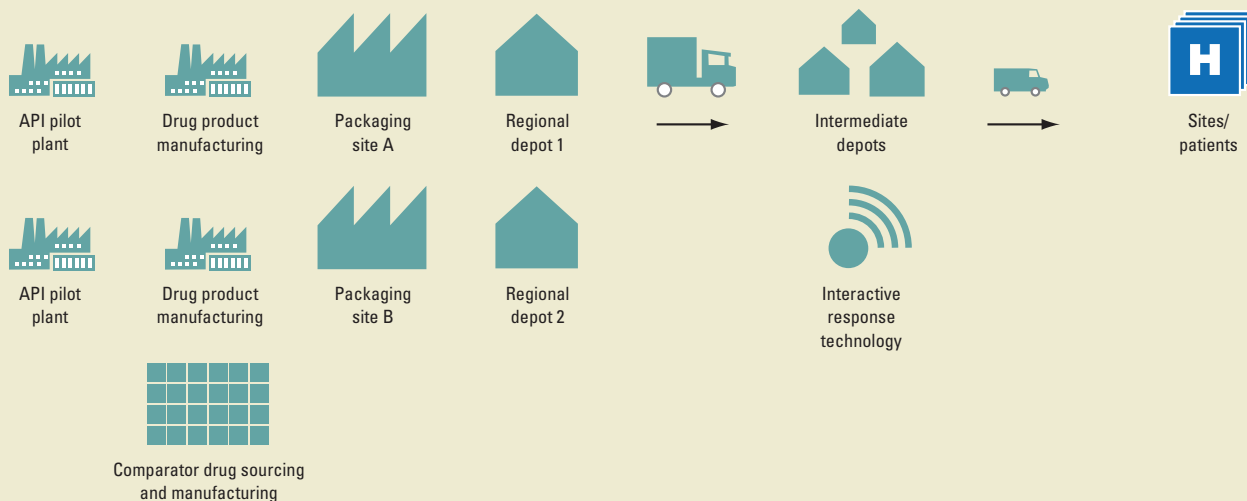
## Challenges of the Clinical Supply Chain

Figure 2 (see page 40) shows the traditional model of the R&D supply chain that is highlighted in this article. Beside physical manufacturing and logistics activities, outsourced services can be used for the coordination of clinical sites. Interactive response technology (IRT) service providers exist as an integral part of global CROs or as specific IT service providers. Regardless of whether the activity is internally executed or outsourced, sponsors and contractors need to overcome many

Figure 1: Increase in novel plausible targets will lead to rapid growth of clinical trial operations



**Figure 2: Traditional model of R&D supply chain**



Source: Lodestone MC

operational challenges in forecasting and planning, manufacturing and warehousing and distribution:

**Forecasting and Planning**

When the trial begins, a range of factors inevitably alter original forecasts and impact planning. The following four factors are key challenges for ongoing trial forecasting and planning.

Patient recruitment varies across sites owing to patient availability, withdrawals, study extensions, investigator performance and other factors. Due to ‘islands of information’, monitoring of the patient enrolment leads a limited exchange of actual patient enrolment data, with the R&D supply chain function to keep supply synchronised with study needs. Figure 3 shows a generic profile of an actual enrolment rate that deviates from planned enrolments.

Long-term stability is a challenge as in many cases API and drug product must be manufactured prior to the availability of long-term stability data.

Inventory visibility at contractor sites is lacking when they keep the inventory for the sponsor in a single step without exchanging full data.

Integration of plans across manufacturing steps is a weakness in most end-to-end supply chains. As stated above, contractors only manage specific parts of the supply chain. Any lead time or delay of planning or status information can negatively impact the entire supply chain.

**Chemical/Biotech Production, Pharmaceutical Production**

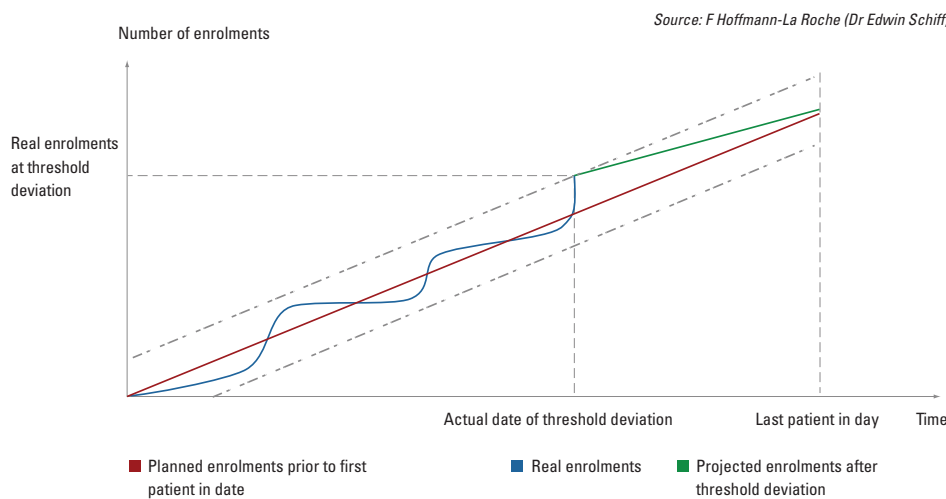
The production of clinical supplies mirrors the manufacturing of commercial drugs in many ways. For example, all operations and processes must be fully compliant with clinical good manufacturing process guidelines (cGMPs), and are subject to audit by regulatory bodies such as the FDA. However, clinical manufacturing – both internal and external – faces distinct

challenges, including unreliable production or supply of API or biotech bulk and manufacture of different dosages and placebos.

**Clinical Packaging**

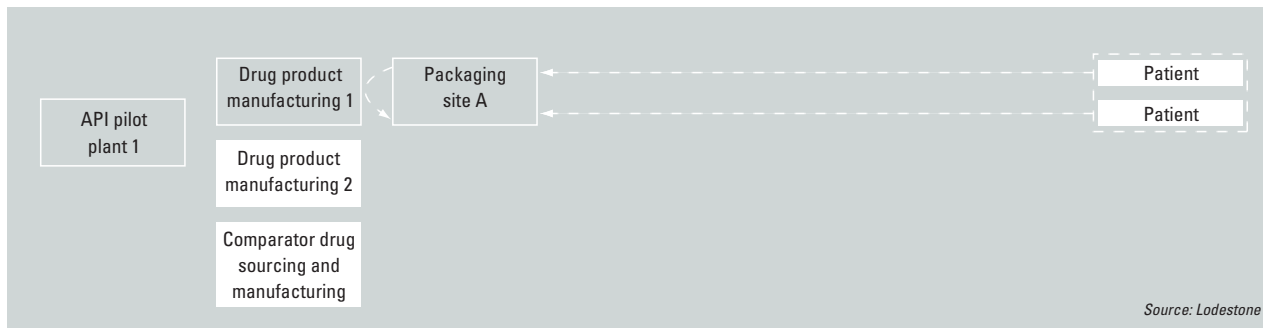
Clinical packaging operations are, in certain cases, a commodity that is outsourced, but subcontractors still face challenges to provide efficient and integrated solutions. Sponsors have also insourced packaging to realise benefits from clinical supply chain integration. Translation of protocols into packaging needs and obtaining approval from clinical operations on complex packaging designs is awkward and requires several iterations to make sure the designs match the needs.

**Figure 3: Actual versus planned enrolments**



Source: F Hoffmann-La Roche (Dr Edwin Schiff)

**Figure 4: Patient oriented R&D supply chain**



Source: Lodestone

A high volume of GMP information is required for a packaging order. Currently, companies need to re-enter such data multiple times due to separation of solutions. Repackaging and relabelling when an extended shelf-life is required. Quality-sensitive data need to be retrieved from various functions. Manual processes are error-prone and induce compliance risks. Use of new technologies is slowly introduced when it can improve quality control, such as label print verification and scanning on the shop floor.

**Distribution**

The shipment of IMPs to many different countries has become a highly niche and specialised operation. Many companies still have cumbersome processes:

- Twenty-four-hour recall requires upstream tracking of API and drug product (DP) batch information. Currently distribution vendors don't have full visibility of the upstream supply chain for a recall which requires crisis teams and multiple data consolidations between sponsors and contractors
- Drug accountability is still expensive and managed by study teams. There are limited solutions that approach the drug accountability with cross-study standardised processes
- Distribution planning is typically managed by the study team and based on a single IRT/IxRS contract. Due to a lack of cross-study inventory data at distribution depots, it is difficult to standardise replenishment planning
- Expiry dating on the IMP label is complex in clinical trials as companies – especially in Europe – are still conservative in the interpretation of health authority guidelines. Health

authorities are also challenging sponsors as their processes for the updating of expiry dates, for example audit trial, is poor

**Clinical Trial Supply Management (CTSM) Process**

Sponsors have a broad range of clinical studies with different supply chain characteristics. As every sponsor company has different priorities, one solution will not fit all needs. For the contractor, this means for sure that his capabilities will need to be multi-functional in order to be successful. Different models exist for rethinking of the R&D supply chain. In some companies even multiple models should co-exist.

**Virtual R&D Supply Chains**

Sponsors can have specialist therapies that require the outsourcing of the entire R&D supply chain from production of the earliest technical batches to IMP packaging and distribution. A number of small research firms have already taken the virtual route, but large companies have also announced plans to outsource a bigger share of their supply chain. It enables a sponsor to shift to a flexible cost base, reduce the risks associated with investing in new assets and access new technologies and skills. For large biotech and pharma companies, executing this strategy successfully involves building a network of fully integrated supply partners that exchange information seamlessly.

**Patient Oriented R&D Supply Chain**

This supply chain is very innovative compared to actual clinical packaging and distribution solutions. Many companies are currently investigating

this model in order to increase flexibility and to lower operational costs. The drug product, such as vial or blister, has a unique code identifier to enable the compliance requirements in packaging blinding and ensuring correctness of treatments. Actual subject enrolment data in the site is continuously monitored and forwarded to the packaging organisation in order to determine the actual IMP need.

The supply chain organisation will have to understand its role towards clinical operations in a much broader sense as it needs to consider the patient in the clinical site as the ultimate customer.

**Full Service R&D Supply Chain**

Companies such as Roche and AMGEN have developed standardised processes with full internal accountability across multiple steps. The supply chain organisation becomes a full service partner towards clinical operations.

Organisations that choose this option will have to make major cultural changes. A supply chain organisation needs to manage demand and supply and establish contractor service level agreements. Such a supply chain has cross-study performance measurement but it is able to manage the different types of studies within channels, such as the on-demand labelling, direct-to-site shipment and conventional distribution through local depots.

The above models require significant changes from sponsor and contractor from an organisational and process perspective. There is no one single technology solution existing that matches above business requirements.

Therefore a CTSM architecture needs to be developed as an integrated architecture of multiple software systems using point solution vendor solutions, IRT/IxRS providers and ERP enterprise resource planning based CTSM solutions (see Figure 6).

The CTSM solutions market is a niche domain. IRT systems cover only the downstream part of the supply chain. ERP-based CTSM solutions have broad functionality including down-stream distribution functionality for depot and site control. However there are limited vendors who can deliver this capability. Point solution vendors provide user-friendly functionality but do not enable end-to-end supply chain functionality.

**Demand Planning and Supply**

Demand modelling functionality enables the initial forecasting and subsequent subject enrolment. Long- and medium-term clinical forecasting should drive drug substance and/or IMP level plans for a make-to-stock strategy. In the short term, the demand forecast is developed at each distribution point supplying to sites. Site level forecasting is even more granular.

A collaborative planning framework will empower clinical supply professionals to integrate the actions and objectives of their outsourced clinical logistics functions. Several functionalities are required to achieve this in clinical trials: what-if analyses, distribution replenishment planning, pooled drug product planning enabling just-in-time packaging, and batch expiry data in supply plans.

**Chemical/Biotech Production, Pharmaceutical Production**

Process-order handling on the shop floor supports GMP. Shop-floor data collection systems, using barcode scanning devices, help to manage the execution of manufacturing and to automate traceability. Batch functionality covers the allocation and tracking of batches to process orders in every production step.

**Clinical Packaging**

Management of labelling involves the design and approval of labels that can be used for a study and/or participating countries. Label printing needs to be integrated with process order handling to ensure seamless data processing.

On-demand packaging or just-in-time labelling allows dynamic fulfilment of supply requests for a study either on demand or from stock. This method assumes streamlined quality control during packaging and labelling across multiple orders to re-supply different sites. Seamless data exchange between contract packager and sponsor or direct access to sponsor CTSM processes provides information visibility.

**Warehousing and Distribution**

The interaction between depot warehouse and order management needs to be automated for compliance and cost control. Multi-level warehouse management and shipping is driven by consignment requests for serialised kits and this requires highly automated process controls to avoid errors in picking of multi-level kits. Cold-chain

shipper time measurement and temperature deviation logging are options for cold chain shipping.

Centralised unblinding provides automatic alerts of an unblinding event by fax or email. Only specifically indicated study personnel have access to the unblinded data.

**Subject Enrolment and Site Stock Control**

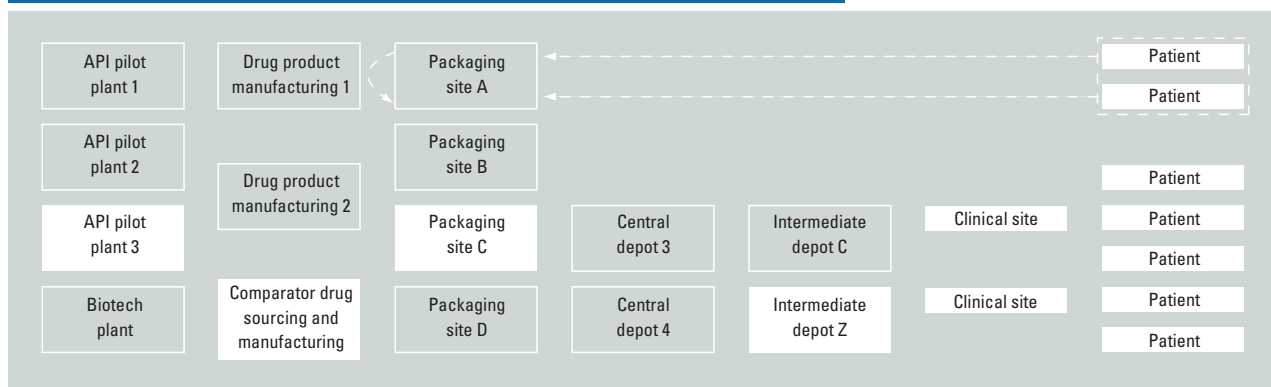
Site stock control provides visibility on inventory information in sites, allowing employees to manage site inventories and report inventory needs and current status by using IRT. Stock control triggers with parameters such as level, buffer levels and visit projection windows reduce waste. Information regarding threshold days until stock-out and current screen-fail rate for example, allows better prediction of site supply needs.

Patient allocation is the process of individual assignment to treatment arms and their respective kit type IDs. The patient code is also applied in medical records. Investigators furthermore maintain a patient diary to keep track of the patient's history and to improve advice during future visits.

**Conclusions and Recommendations**

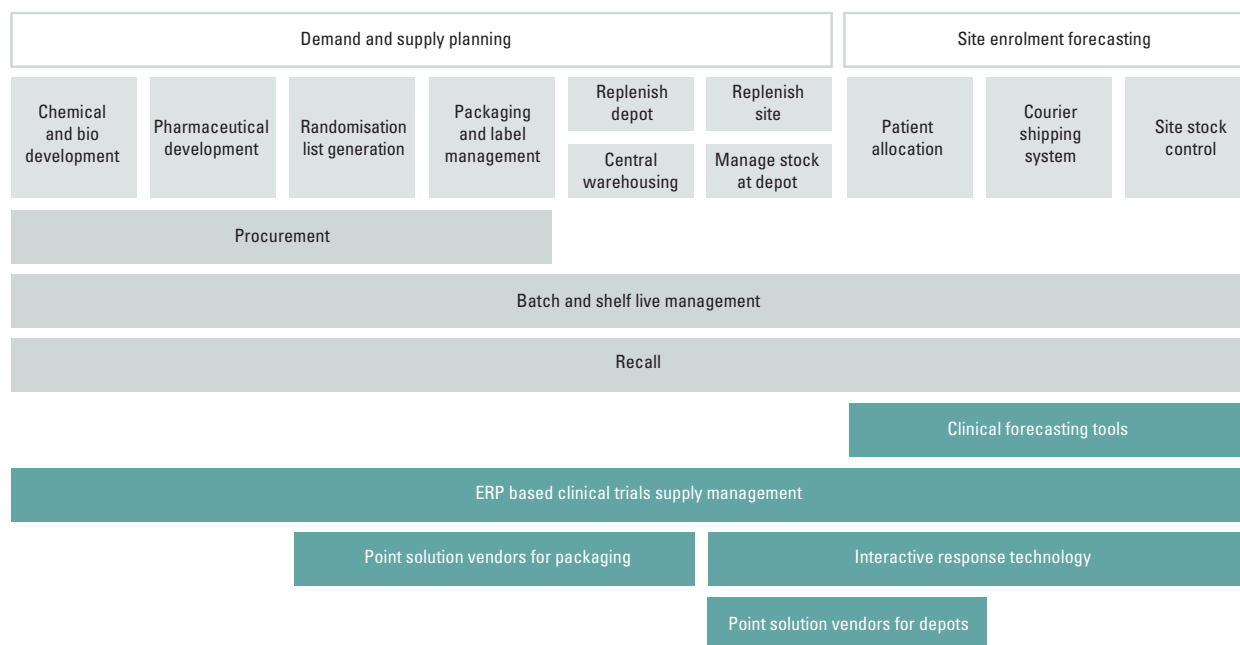
A significant opportunity exists for life science sponsors and contractors to improve the efficiency and cost effectiveness of outsourced clinical supply activities. In the most successful cases, companies have

Figure 5: Full service R&D supply chain (white boxes are managed by contractors)



Source: Lodestone MC

**Figure 6: Solution map identifying roles of internal functions and contractors**



Source: Lodestone MC

started with a clear vision and a solid business case.

A comprehensive programme based on revised processes and new technologies, supported by a change management programme and organisational transformation, is the key to managing an extended clinical supply chain. The vision should not be just another improvement but a transformational answer to future trends, such as:

- Health authority guidelines increasingly referring to opportunities to use electronic means
- Adaptive study designs and new target diseases will require on-demand labelling and supply strategies

An integrated approach towards best in class internal and external CTSM processes supported by state of the art technology will result in reduced time-to-market, shortened study timelines and reduced R&D costs.

**Further Reading**

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6. FDA, Guidance for Industry Process Validation: General Principles and Practices, November 2008

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