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Managing the Extended R&D Supply Chain

by Petra Bielmeier and Geert Crauwels

This article presents the R&D 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.

Increasing Business Pressures

Most recent research on clinical trials focuses on the outsourced Research and Development (R&D) activities, such as data delivery, site conduct, and development. This article describes, 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 as the pharmaceutical industry and its needs have changed. New technologies and target diseases require more complex trials and in search of patient mass and lower cost, the clinical trial base has shifted toward markets such as India and China.

This has driven a drive for scale in some leading Clinical Research Organizations (CROs) and the emergence of truly global players, while others have responded by focusing in emerging markets, adding niche and specialized 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 often 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 realized.

Sponsors remain accountable for their clinical trials and also need to rethink and/or develop the R&D supply chain.

Streamlining Clinical Trials

Clinical trials are an essential part of the drug development process and if run efficiently can provide the pharmaceutical/biotech company with a competitive advantage. Many internal

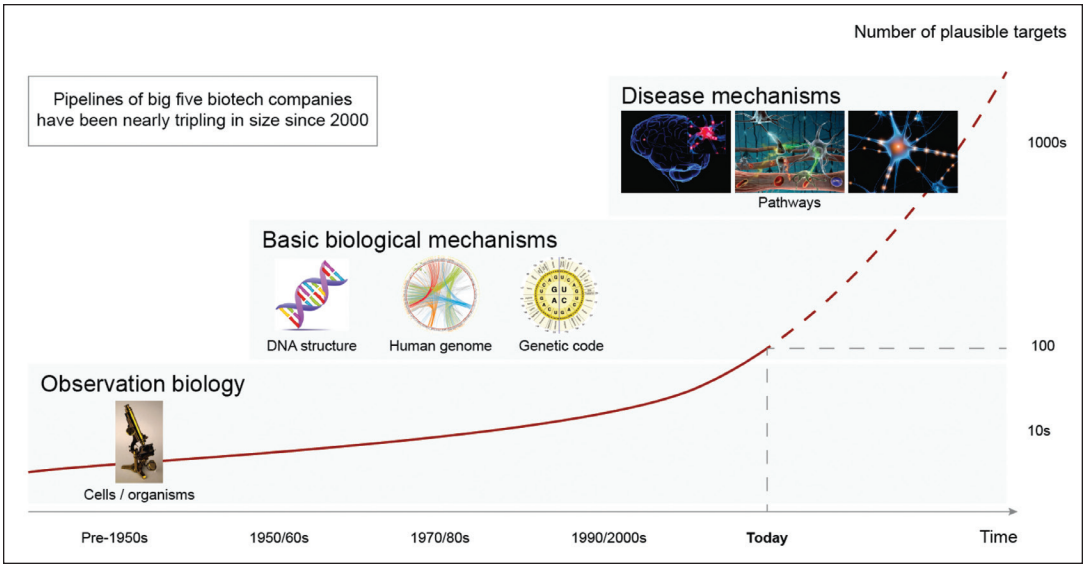

Figure 1. Increase in novel plausible targets will lead to rapid growth of clinical trial operations (Source: Lodestone).

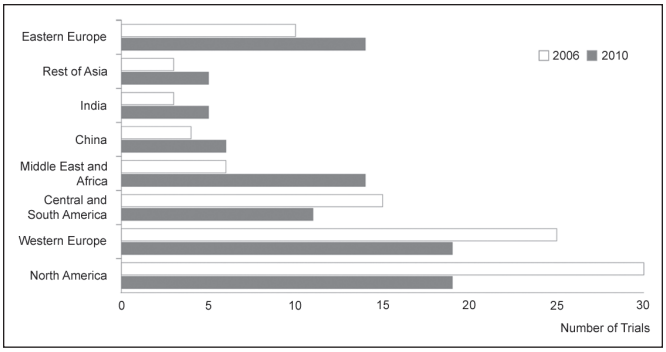

Figure 2. Evolution of trials from 2006 to 2010 by region – Source Gartner (Steven Lefebure).

and external company stakeholders point to developments costs as a barrier to innovation. The US Food and Drug Administration (FDA) has confirmed as part of its "Critical Path Initiative" that "streamlining clinical trials" is one of its key priorities.[1]

The shift toward global trials adds a further layer of complexity to the clinical supply chain[2]; therefore, companies must be able to manage both global and local regulatory requirements.

However, regulatory guidelines describe measures to protect patient safety, but not necessarily how to conduct trials. An effective operating model that supports integrated processes, inventory visibility, and compliance in manufacturing and distribution of clinical trial supplies becomes a priority. The integration of contractors in the R&D supply chain has been underestimated in many outsourcing strategies. Also contractors are not profitable enough to ensure sustainable growth and to put capabilities in place in order to deal with future challenges. This constitutes a considerable industry risk.

Future risk assessments need to differentiate between smaller life sciences companies and big pharmaceutical/biotech sponsors. Outsourcing of almost the complete study supply chain will be increasingly attractive to smaller companies who need the critical mass and footprint of global contractors. Big biotech and pharmaceutical sponsors require the highest levels of transparency and compliance in their global harmonized R&D supply chains, and will likely maintain clinical trials supply in-house in combination with outsourcing.

Contractors will make contributions in specific steps and they will need to establish new capabilities for collaborating with sponsors. Beside the externalization of physical manufacturing and logistics activities, outsourced services can be used for the coordination of stocks and enrollments at clinical sites. Their relationships and integration touch points are specific by category:

- API and DP contract manufacturing: prior to the point of finished goods packaging, the R&D supply chain employs a number of contract manufacturers for API and DP. Integration touch points between both parties include details about material inventory, including status, location, and quantity updates. The sponsor provides supply requirement plans and details about manufacturing orders, including bill of materials and detailed order instructions. The contractor is typically accountable for all ingredient batch traceability unless sponsor material is provided to the contractor.
- Third party logistics: API, raw materials, and drug product need to be moved through the supply chain. The transfer requests and confirmations are exchanged between sponsor and contractors. Also "cold chain aspects" are part of the information flow, especially the decision making in case of deviations.
- Contract packaging and labeling of clinical finished goods: the information exchange between sponsor and contractor is similar as for API and DP manufacturing. The blinding of IMP requires exchange of label samples and package numbers. Complex packaging designs and work instructions need to be specified and provided to co-packers for every clinical trial.
- Third party clinical finished goods distribution: clinical depots are located across the globe. Many low-volume pick, pack, and shipment operations (thousands of patients can participate in a study) are executed by multiple logistics providers. Inventory quantity, package numbers, and

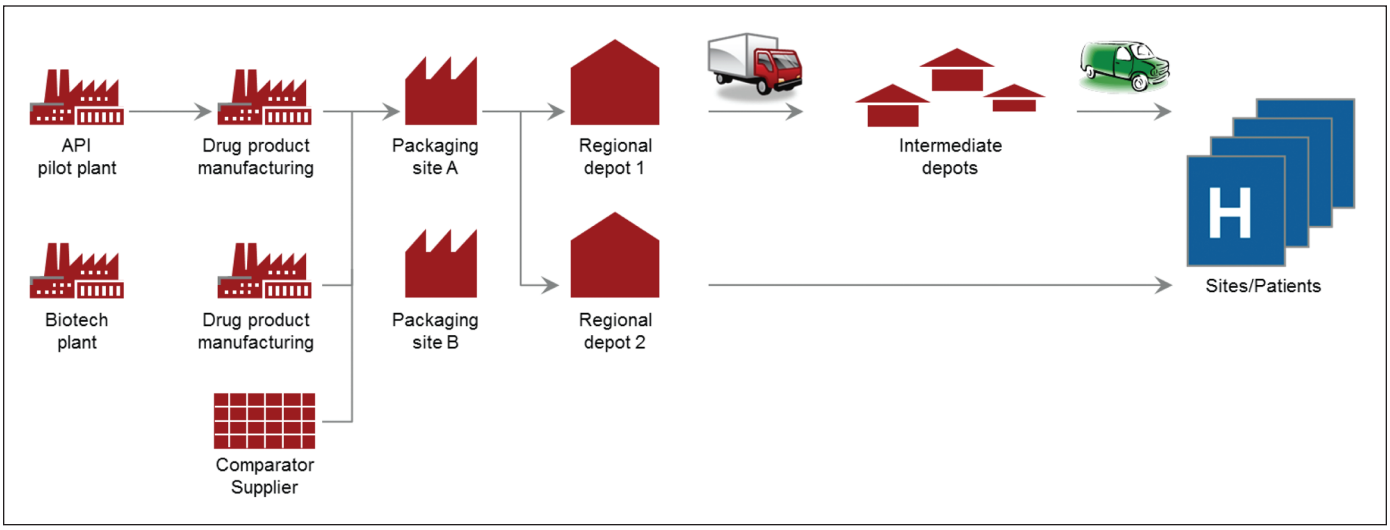

Figure 3. The R&D supply chain (Source: Lodestone).

status information are continuously shared for planning and traceability purposes. Also in this area, extensive cold chain information needs to be exchanged.

- Site stock control: stocks and enrollment information at clinical sites can be handled by external or internal monitors. Study teams need this information to manage the site supply which can be captured and exchanged in multiple ways. Drug Accountability (DA) systems and Interactive Response Technology (IRT) are typically used for high volume and global studies. Sponsors can use external service providers that provide this technology including the staff required to manage the IMP supply to and in the sites.

The Challenges of the R&D Supply Chain

Figure 3 shows the end to end supply chain. First, the API and DP manufacturing in the upstream part of the R&D supply chain is part of the "technical development" organization. It is a silo type organization with departments that have a science focus on the development of API and DP. "Manufacturing process science" is obviously a key deliverable from those departments, but world-class performance results in "manufacturing compliance, speed, and cost effectiveness" are still far from reality. Comparator drug manufacturing can be defined as a normal "DP manufacturer," but dynamics are different as DP is typically sourced via intermediate entities and it drives the study supply costs significantly. The packaging unit for IMP is dealing with blinding aspects of the trial.

Second, Figure 3 shows that components can be provided from different sources and IMP is transferred to a distribution network.

As depicted in Figure 3, further downstream in the R&D supply chain, a complex clinical distribution network is established for each study. The distribution ends at the patient visit in clinical centers or sites, potentially managed with interactive response technology from CROs or specific IRT service providers. This distribution network is also dealing with several complexity challenges that will be further described in this paragraph.

Regardless if the activity is internally executed or outsourced, sponsors and contractors need to overcome many operational challenges in forecasting and planning, manufacturing, and warehousing and distribution for active pharmaceutical ingredient, drug product, and clinical finished goods.

Forecasting and Planning

This process has different planning levels and horizons. It also has two modes: before and after study initiation. The following four factors are key challenges for ongoing trial forecasting and planning:

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.

Patient recruitment: when the trial begins, a range of factors inevitably alters original forecasts and impacts planning. Enrollment varies across sites owing to patient availability, withdrawals, study extensions, investigator performance, and other factors. The monitoring of patient enrollments is typical available information, but it is difficult to access by the R&D supply chain function. The actual enrollments should be considered to produce any demand data for re-supply of IMP. Otherwise planning becomes a very ineffective process. Figure 4 shows the generic profile of an actual enrollment rate that starts deviating from planned enrollments.

Inventory visibility at contractors 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 supplies for clinical use mirrors the manufacturing of commercial drugs in many ways. For example, all operations and processes must be fully compliant with current Good Manufacturing Practices (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. The "demand" is defined for R&D projects or studies driving either clinical or non-clinical demand. A non-clinical product is still in its "science status" meaning that the recipe is still dynamic. A clinical product has the purpose to be used for clinical trials; however, it can end up as a restricted for certain or all studies.

Clinical Packaging

Clinical packaging operations are in certain cases a commodity that is outsourced. For example, high volume open label study material is typically outsourced; however, subcontractors have still challenges to provide efficient and integrated solutions. Sponsors keep typically low volume studies in-house as the management costs for outsourcing would be too high, especially for complex studies. Beside this, they also have insourced the packaging to realize benefits from clinical supply chain integration.

Four supply chain integration challenges need consideration in the design and operation of the clinical packaging:

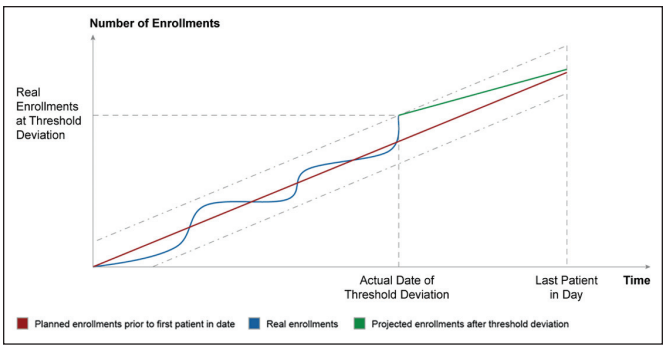

Figure 4. Actual versus planned enrollments (Source: Hoffmann-La Roche (Dr. Edwin Schiff)).

- Translation of protocols into packaging needs and obtaining approval from clinical operations on complex packaging designs is awkward. It requires several iterations to make sure that the designs match the needs. A protocol has typically multiple treatment groups, countries, and possibly different study phases. Different packaging types (e.g., comparator versus active, multiple visits) are used for the dispensing of IMP to patients. The IMP can have a bill of material with several levels and many components. Clinical supply coordinators have to make sure that the requirements from the study team are correctly translated into this packaging data. This information needs to be properly shared across departments and possibly company borders. As protocols are approved only a limited period before the first patient visit, it is important to ensure seamless data exchange, ideally with a graphical representation of the packaging design and labels in order to avoid misunderstandings between study team and packaging.
- 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. A packaging order is not a simple instruction to produce a quantity of a certain kit assembly by a due date. It is a very comprehensive set of GMP relevant information, for example: along with the various master label design information, each component label that is used in the kit needs to be printed with the package number of the kit. Work instructions - that are study and material specific - must describe in detail what needs to be executed by the packaging operator. A specific label must be applied on a component in the bill of material. The distribution center requires the link between the license plate number of the outer box carrying all package numbers. This high volume data generated by packaging is in many companies still manually registered. The cost of verifying the quality of multiple data sources is too high; therefore, a single entry and secure distribution of data needs to be implemented.
- Introduction of new packaging and labeling technologies to improve quality control. Reliable technologies are available on the market while many companies have still manual work methods, even for high volume packaging. For example, label print verification can be integrated in the label printing process. It provides automatic feedback for re-printing of labels. This avoids rework or correction during the packaging process. Also in-line printing of labels during packaging doesn't require witnessing by peers and post label reconciliation as the labels are only printed at the time that a kit is assembled.
- Re-labeling or over-labeling is necessary when a product is expired. The process starts with a shelf-life prolongation request and approval. Once the new retest date or use-by-date is approved, the data must be forwarded to multiple parties, such as the in-house or outsourced label room, internal or external packaging or distribution location where the IMP is located, quality people who review and approve the re-label operations, etc. Manual processes such as emails are error-prone and induce compliance risks; therefore, a validated system needs to be in place for this process.

Distribution

The shipment of IMP to many different countries became a highly niche and specialized operation. Many companies have still cumbersome processes:

- 24-hours-recall requires upstream tracking of API and 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 standardized processes.
- Distribution planning is typically managed by the study team and based on a single IRT/IxRS contract. Due to lack of cross-study inventory data at distribution depots, it is difficult to standardize 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 expiry date updating, for example, audit trial, is poor.

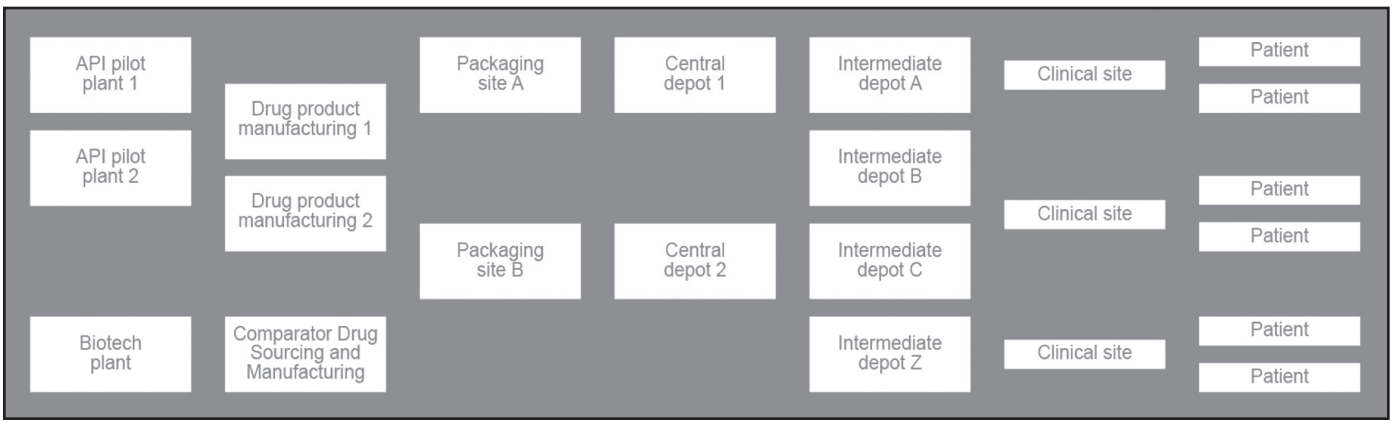

Figure 5. External R&D manufacturer with network of fully integrated supply partners (Source: Lodestone).

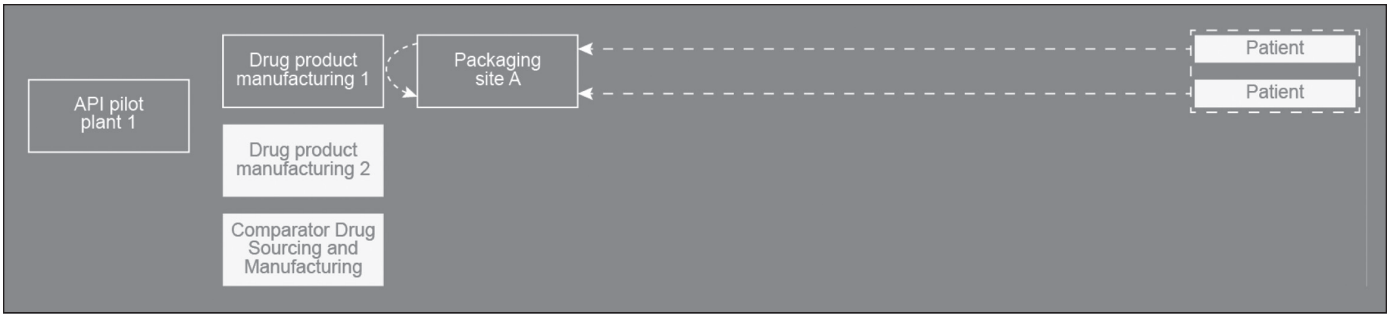

Figure 6. Patient oriented R&D supply chain (Source: Lodestone).

CTSM Process, Organization, and Technology Options

Sponsors have a broad range of clinical studies with different supply chain characteristics. As every sponsor company has different priorities, not "one solution will fit all needs." For the contractors, this means for sure that their capabilities will need to be multi-functional in order to be successful.

Different Supply Chain Models

Different models exist for rethinking of the R&D supply chain. In some companies, even multiple models should co-exist.

Externalized R&D Supply Chains

Sponsors can have specialist therapies that require outsourcing the entire physical 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 external route, but also large companies have 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 pharmaceuticals, executing this strategy successfully involves building a network of fully integrated supply partners that exchange information seamlessly - *Figure 5*. Information of the R&D supply chain is virtualized as external organizations are enhancing and updating data. The sponsor needs still this virtual generated information to plan and to control the external supply chain. This will become one of the key challenges in the externalization as the number of studies is increasing and globalization is the overall industry trend.

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 of patient delivery and to lower operational costs - *Figure 6*.

This model will require complete new ways of working in the production of drug product and IMP. This article highlights three building blocks as possible pillars for future solutions:

1. Drug product identification: the drug product has a unique code identifier to enable the compliance requirements in packaging blinding and ensuring correctness of treatments - *Figure 7*. Even the formulation of the drug product can become patient specific. The reader should remark here that this concept is not only about serializing the IMP and its components at the time of packaging. The drug product is serialized at the time of its production. This is not a common practice at the time of publication. Only pilots are implemented in the industry.
2. Zero-stocks: actual subject enrollment data in the site is continuously/real-time monitored and forwarded to the packaging organization in order to determine the actual IMP need at the packaging supply node. This is already a common practice at the moment of publication, but there are no pilots with zero IMP stock policies in hubs or intermediate depots.
3. Site and packaging control system: in this patient driven supply chain, systems such as IxRS will become obsolete and another solution will be required. A request is created and allocated to a single patient. The packaging order is directly linked to a patient.

The above examples are "just" business methods and must be seen in an extended context. The supply chain organization will have to understand its role toward clinical operations in a much more broad sense as it needs to understand the patient behavior in the clinical site as the ultimate customer.

Full Service R&D Supply Chain

Companies have developed standardized processes with full

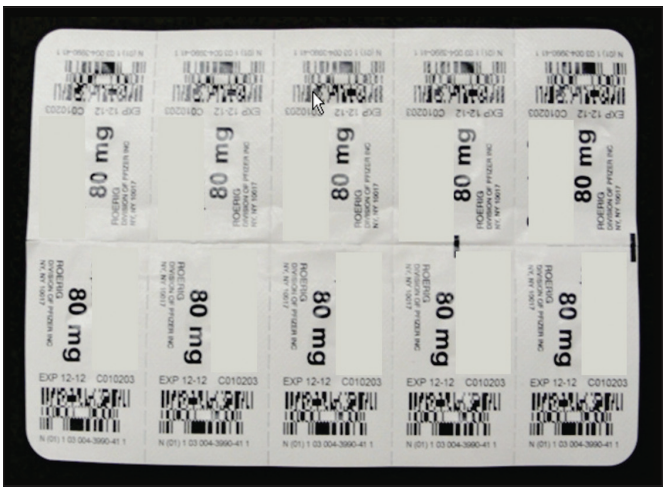

Figure 7. Coding of drug product and primary packs (Source: Lodestone).

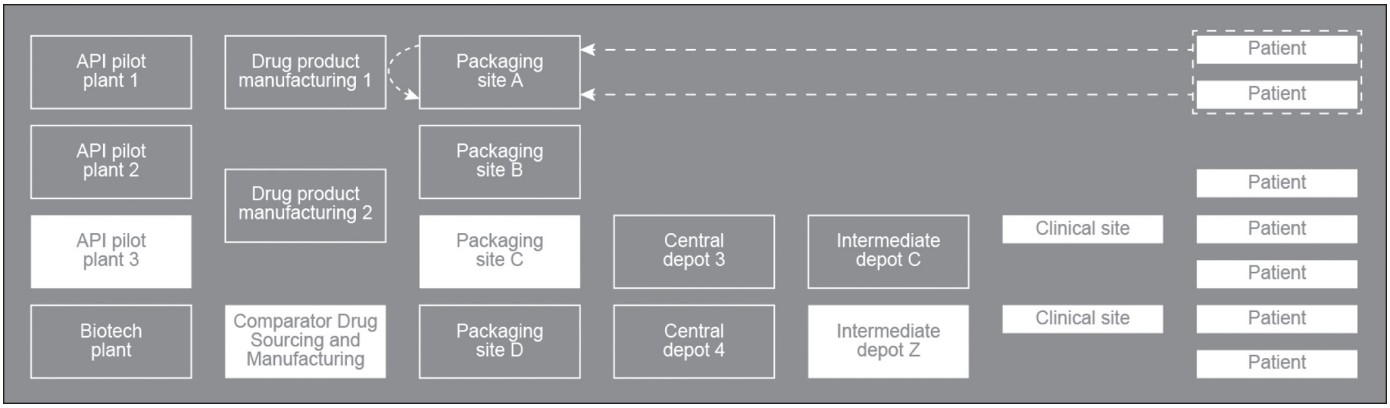

Figure 8. Full service R&D supply chain (Source: Lodestone).

internal accountability across multiple steps including the clinical distribution. The supply chain organization becomes a full service partner towards clinical operations - *Figure 8*.

Organizations that choose this option will have to make major cultural changes. A "supply chain organization" needs to manage demand and supply for multiple models and types of studies 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 patient oriented supply, direct to site shipment either from stock or on demand and conventional distribution through local depots, outsourcing of specific steps depending on study needs.

Direct to site shipment from regional hubs became already a more common approach in the last few years in order to eliminate the intermediate storage lead time at local or country specific depots; however, on-demand packaging has not been fully deployed across the industry. On-demand allows dynamic fulfillment of requests for a study at the moment that the order has been provided. The final IMP is not yet existing at the time of the request. The "stocking" of the drug product or other intermediate product form allows to create the final IMP in a very short lead time, either in a packaging center, regional hub, or final/country depot. The next paragraph will describe the on-demand method in more detail.

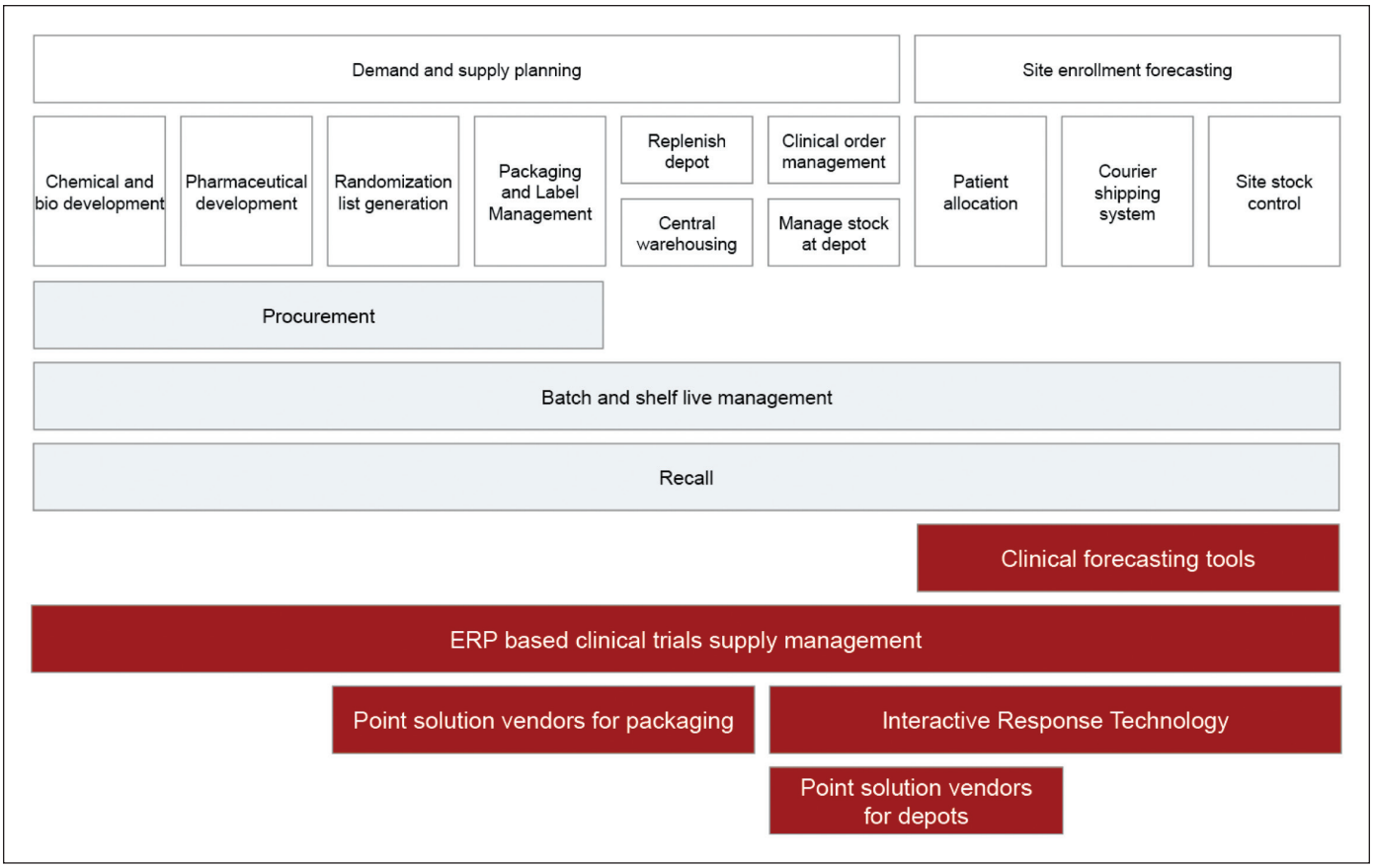

Figure 9. Solution map identifying roles of internal functions and contractors (Source: Lodestone).

Business Solutions Architecture for R&D Supply Chain

All above models will require major changes at sponsor and contractor, from an organizational and process perspective. There is no one single solution existing that matches above business requirements; therefore, an "architecture" needs to be developed as an integrated architecture of multiple systems using point solutions, IRT/IxRS providers, and ERP enterprise resource planning based CTSM solutions - *Figure 9*.

The solutions market for R&D supply chain is a niche domain. IRT systems and Drug Accountability systems cover only the downstream part of the supply chain. Many IRT vendors can offer bundled services, but operate only on study level. 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 and Supply Planning

Although this article is advocating the need of on-demand packaging and labeling and the future development of a patient oriented supply chain solution, there is still the need for planning. Planning is not in contradiction with on-demand packaging. The right method must be deployed in the right supply chain segment.

Demand modeling functionality requires different horizons of forecasting. Long/medium-term clinical forecasting should be used for DS, DP, and/or IMP level planning with a make-to-stock strategy. The demand feeds conventional materials requirements planning while clinical batch data are considering study and country characteristics and the expiration of stocks. On the short term, the demand forecast is aggregated at each distribution point that is 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, drug product planning enabling just-in-time packaging, batch data in supply plans.

The above topics have many different variants. Recent analysis with sponsor companies has proven that deterministic forecasting, overlaid with actual enrollment data from the sites, leads to reduced overage, minimal safety stocks, and supply lead time.

The deterministic forecasting feeds the replenishment planning for a depot or hub or complex distribution network that deals with many studies and sites. Replenishment planning is based on the following building blocks:

1. Safety stock algorithm: based on the study demand which considers all enrollments in all sites. So even if the number of sites is very high, the demand will consider all site needs, respectively also the safety stock in the depot will be relatively important.
2. Depot replenishment: the enrollments and all finished goods stocks are netted on a frequent, e.g., weekly basis. In case that the dispensing of stocks in a site is faster than expected (which is very unlikely as the actual enrollments are considered in the depot replenishment planning), there is still the use of safety stock in depot.
3. Site replenishment: the enrollments and site stocks are netted continuously, e.g., daily. This site replenishment process is cascading with the depot replenishment planning process.
4. Ad-hoc stock investigation: in case of exception handling, a total stock report provides details to take actions separately from above weekly and daily planning activities.
5. Clinical batch information is required for expiration, country and study restrictions.

The above forecasting and planning techniques can be complemented by stochastic forecasting. While deterministic forecasting is a frequent repeating process using average values, stochastistic forecasting takes into account the variability of clinical trial parameters such as titration/dropout and stratum. Variability has a significant impact on the clinical trial supply chain. The technique allows to reduce the overage and the risk of running out of stock. The main goals of a stochastic engine are to optimize costs, to define the optimal IMP safety stocks, and re-supply lot-sizes and frequencies; however, this technique is resource intensive in case it is used for all studies at a company.

As a summary, the best practice demand and supply planning framework has the following characteristics:

- Long/medium-term clinical forecasting
- Short term demand forecast at each distribution point and site level forecasting
- Deterministic forecasting complemented by stochastic forecasting for complex studies
- Replenishment planning at depot and site level
- Clinical batch data considering study and country characteristics and expiration data

Chemical/Biotech Production, Pharmaceutical Production

Process-order handling on the shop floor supports the need for GMP information. Shop-floor data collection systems, using barcode scanning devices, help to manage the execution of manufacturing and to automate traceability.

Batch management functionality covers the allocation and tracking of batches to process orders in every production step.

Moreover, the integration with external partners is critical to ensure visibility of inventory and traceability across the R&D supply chain.

Clinical Packaging and Labeling

First, this section highlights the specifics of clinical labeling, packaging, and randomization. Second, the importance of on-demand or just-in-time packaging is stressed in order to deal with future business trends. Finally, this evolution is put in

the context of the extended supply chain.

Labeling management is the design and approval of labels for a study and/or participating countries. Electronic routing and approval of labels is important due to the multiple hand-overs and iterations. Label variable data should be integrated with process order handling to ensure seamless data processing.

Packaging needs to deal with initial and on-going supply. At initial supply, the IMP is stored to deal with the uncertainty of unexpected demand as site activations are not 100% predictable. On-going supply needs to avoid any stock-out while expiration is a key constraint.

Creation and handling of randomization lists is complex as multiple parties need to be involved. The randomization solution could be incorporated in the packaging operations and provide access for the biostatistician and possibly IxRS vendor, or in general, the list must be electronically routed and approved by multiple stakeholders.

On-demand or just-in-time packaging will increase importance in the industry in order to reduce batch expiration and re-labeling costs. New trends in clinical studies will require that batches can be re-supplied more frequently or even immediately for a site request or individual patient need.

On-demand or just-in-time packaging allows dynamic fulfillment of IMP requests for a study. This means that IMP stocks are not on-hand available for the requester. This on-demand method can be deployed in many variants and combinations:

- Use at different location types: the method is not always executed in a packaging center facility. It can be used at hubs or local depots.
- Use of pooling: investigational medication product stocks will be stored independently of the protocols requiring it. At the receipt of order, the protocol is added to the IMP identification.
- Label printing only at receipt of site request: this method avoids use of expensive booklet labels (booklets are used in order to share stocks across countries).
- Use of on-hand stock of drug product or other intermediates: as IMP is immediately packed the drug product or other intermediates must be planned according to a make-to-stock strategy.

For the use of above methods, packaging and labeling operations are highly impacted. They require more advanced solutions, such as following solution building blocks:

1. Electronic batch recording will reduce the "records review" effort on the shop-floor and will shorten the lead times of batch record handling.
2. On-line printing prints the label during the packaging which eliminates the label room storage or external label printing services from a printer vendor, especially if the booklets are leading to high operating costs, label reconciliation tasks, and human witnessing of label application is also labor intensive.
3. Streamlined batch management is an advanced quality control method during the packaging and labeling across multiple orders to re-supply frequently. Orders are executed for multiple countries. The streamlined batch solution avoids that the sampling and batch record handling will lead to uneconomic packaging and quality operations. There is no industrial use of this method yet at the moment of publication; however, this new business method will only be used once the clinical supply business and regulatory agencies mature.

Seamless data exchange between contract packager and sponsor or direct access to sponsor processes provides information visibility. Conventional packaging, labeling, and randomization techniques requires frequent and complex exchange of above data contractors. Just-in-time packaging will even increase the complexity to this data exchange model.

Warehousing and Distribution

The integration between depot warehouse and order management needs to be automated for compliance and cost control. New techniques such as portal technology allows to connect the external partners to the sponsor inventory backbone.

Multi-level warehouse management and shipping is driven by consignment requests for serialized kits. This requires highly automated process controls to avoid errors when selecting multi-level kits.

Cold-chain shipper time measurement and temperature deviation logging are methods applied in cold material handling. Sponsor pipeline products are becoming increasingly cold chain with the influx of biomolecules and management of these items. Their temperature excursion is becoming increasingly costly. It is likely to become a burden for commercial sites as well as these products launch.

The cold chain solution is defining the allowable time by item for a batch operation, monitoring time of individual batch operations, monitoring the temperature along operation, and ensuring deviation logging and resolution. This solution becomes highly complicated in case that cumulating operation time over the lot genealogy is required.

Centralized un-blinding provides automatic alerts of an un-blinding event by fax or e-mail. Only specifically indicated study personnel have access to the un-blinded data.

Subject Enrollment and Site Stock Control

Site stock control is providing visibility on inventory information in sites. Employees managing inventories at sites can 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 such as threshold days until stock-out and current screen-fail rate 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.

Doctors and surgeons data is logged in databases. Patients can check the availability of the concerned doctors or surgeons using IRT.

New Technology Trends

This article highlighted new solutions and business methods that will gain importance for the extended R&D supply chain. New technology trends will change the way how sponsors and contractors will design solutions. There are already references in the industry about the use of R&D supply chain enterprise software. This trend is new as point solutions were not delivering transformational benefits.

Another technology to watch is the "cloud," especially for smaller companies that don't want to invest in assets for supply chain; however, there are no cases found in the industry at this moment of publication.

R&D Supply Chain Enterprise Software

The use of Enterprise Resource Planning (ERP) software has been identified by several biopharma companies as the appropriate technology for increasing transparency of demand and stock levels across the entire supply chain and to ensuring full compliance as well as backward and forward traceability. It is a capability that allows the consolidation of all business processes into a single enterprise-wide environment.

The competitive advantages are:

- Higher service level to the clinical site at optimal cost
- Greater supply responsiveness to changes in demand
- Increased efficiency due to streamlined business processes in the end-to-end supply chain
- Decrease waste due to forecasting techniques and planning of the supply chain including expiry dating visibility

The investment in such ERP depends on the need to modify it. Complex biopharma companies have specific requirements that cannot be standardized in the industry. In such case, the investment is very important and strategic. CROs and subcontractors have less need to modify such solutions which allow to limit the implementation costs.

The Cloud for BioPharma Validated Environments

Biopharma organizations' typical pain point in IT deployment is that it takes a huge amount of testing to fulfill all the computer validation requirements as per the 21 CFR Part 11 guidelines. Testing cycle contributes ~25% of the application deployment cost. The duration of an implementation project in life sciences organization is at least 15% longer than the similar project in other industries. So what are the ways to reduce these timelines, effort, and cost? The types of testing cycles involved in implementation for a life sciences organization are:

- Unit testing
- Informal screening of business scenarios
- End to end integration testing
- Performance testing
- User acceptance testing
- Day-in-a-life test

The formal screening of scenarios is to ensure satisfactory testing as per the regulatory needs and it consumes a lot of testing effort. The business scenarios which are GxP impacted have to be tested formally with extensive documentation which adds up to the testing effort.

Apart from it, it needs hardware to comply with certain installation qualifications which takes more time for environment preparation compared to environments in non-regulatory industries. The cloud eliminates the need of purchasing and maintaining own hardware; however, CROs or sponsors need to ensure that the environment comply with the Installation Qualification (IQ) , Operational Qualification (OQ), and Performance Qualification (PQ) requirements. Several service providers offer a specialized service for the CRO or sponsor reducing the time and cost of the environment preparation in the cloud. While doing so, the CRO or sponsor can proof its accountability, while leveraging external parties to get those requirements fulfilled. So cloud computing will reduce the cost of implementation projects in this matter.

This solution is certainly for fast growing companies that don't have the infrastructure in place or internal resources. In the long term, CROs and subcontractors need to integrate with their life sciences customers who are the sponsor of a clinical trial. Those sponsors have the need to integrate with their chemistry and pharmaceutical development, clinical packaging, and distribution. In the future, many sponsors want to exchange their data with CROs. Many CROs are not professionally organized for that and they will lose business due to lack of integration and transparency. CROs and subcontractors can increase their market share by using the cloud-based applications. First, it will show commitment to customers (big biopharma) as integration with their clients will become critical. Second, it will increase company profitability growth by enhancing CRO capabilities to obtain the sponsor's data and to provide full transparency to the sponsor.

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 started with a clear vision and a solid business case.

They have introduced a comprehensive program based on revised processes and new technologies supported by a change management program and organizational transformation. The vision should not be just another improvement, but a transformational answer to future trends, such as:

- Introduction of a planning framework that considers all elements of integrated planning: all demand and all supply sources. The key challenge is to capture all inventories including batch data across the supply chain.

- Health authority guidelines increasingly refer to opportunities to use "electronic means." A common hurdle to implement new solutions is the system validation. Vendors should mature further by providing "accelerators" for implementation.
- New adaptive study designs, new target diseases, and global studies will require on-demand labeling and packaging methods in order to keep operating costs under control. Methods like streamlined batch management will need to be used. This will require new interpretation of regulatory requirements.

As a conclusion, an integrated approach toward best in class internal and external CTSM processes supported by state of the art technology will result in higher compliance, shortened study timelines, and reduced R&D costs.

Acronyms

API	Active Pharmaceutical Ingredient
cGMP	current Good Manufacturing Practice
CMO	Contracting Manufacturing Organization
CRO	Contracting Research Organization
CTSM	Clinical Trial Supply Management
DP	Drug Product
ERP	Enterprise Resource Planning System
FDA	Food and Drug Administration
GCP	Good Clinical Practice
IMP	Investigational Medicinal Product
IRT	Interactive Response Technologies
JIT	Just-In-Time
I(W)VRS	Interactive Web/Voice Response Systems (also IxRS)
R&D	Research and Development
SAP	SAP is an ERP system that can be used as a platform to build a CTSM solution

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About the Authors

Petra Bielmeier is Head of Global Investigational Product Supply, F. Hoffmann-La Roche Ltd currently based in Basel, Switzerland. As a pharmacist, Bielmeier has had nearly 15 years of experience in various pharmaceutical fields and companies. She is an expert in Global Clinical Supply Chain Strategy and Management. In addition, she is very passionate about Business Process Excellence in Clinical Supply Chain and extremely experienced in working globally. She gained her first experiences at Wülfing Pharma GmbH, a contract manufacturer in Germany. Her main focus was clinical trial supply planning and execution and several projects in the galenical development. She then worked for two years as a Global Trial Coordinator (Project Manager) on several developments projects (Phase I up to global Phase IV) at Hoffmann-La Roche in Basel. From 2003 to 2004, she was Head of the chemical pharmaceutical laboratories in the Quality Control Department as well as deputy Qualified Person at Haupt Pharma GmbH in Germany for small and large molecules. She has been with Hoffmann-La Roche since 2005 in her current role leading the clinical supplies management group globally and being a member of various leadership teams in Technical Operations and TR&D. She can be contacted by email: petra.bielmeier@roche.com.

F. Hoffmann-La Roche AG, Bldg. 204/1003, CH-4070 Basel, Switzerland.

Geert Crauwels is Partner, Global Life Sciences Consulting, Lodestone. Crauwels drives a global services team specialized in supply chain management at Lodestone Management Consultants. The services encompass strategy definition and implementation of clinical supply chain process improvements. In 2008, Crauwels extended the consulting organization with a technology team to develop solutions for the R&D supply chain. The technology - CTSM Add-On Suite for ERP - enables end-to-end supply chain management which is unique in the industry. Crauwels has written several white papers about supply chain management innovation. His current research focuses on virtualization of R&D manufacturing and quality information and on patient oriented R&D supply chains impacting all life sciences stakeholders. He can be contacted by email: geert.crauwels@lodestonemc.com.

Lodestone Management Consultants AG, Obstgartenstrasse 27, Postfach 201, Zurich 8058, Switzerland.