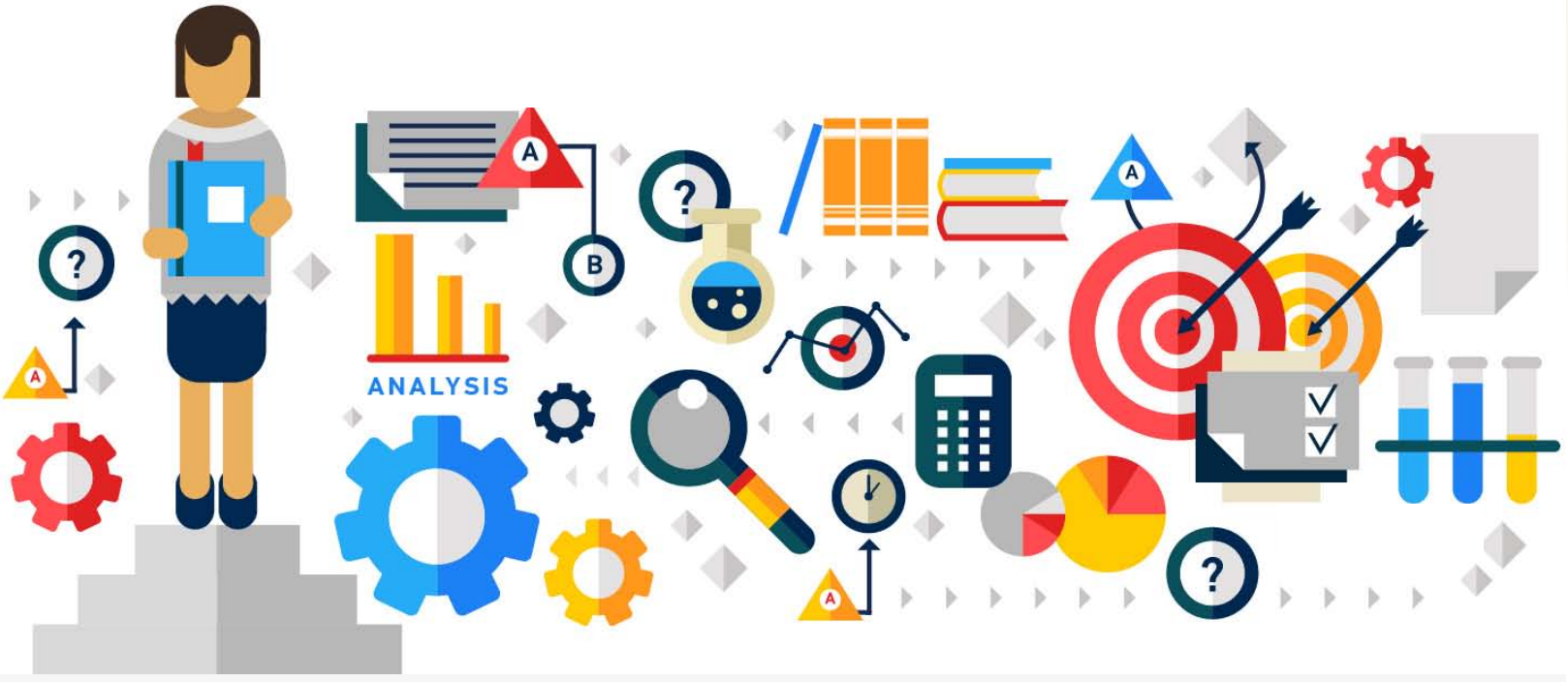
Hurdling the Stumbling Blocks in Clinical Trial Supply



Innovative Technology & Tactics

Featuring industry experts from:

Novo Nordisk
A/S Amgen LTD
PPD
Sanofi

Clinical Trial Supply Europe

Pharma iQ
a division of IQPC

The supply of clinical trials is the one of the most onerous tasks in this pivotal late phase of drug development. The task is further complicated by the ongoing complexity and sheer expanse of the global clinical trial supply chain. Unsurprisingly, efficiency is paramount to ensure there are no delays imposed on the drug reaching the market and, needless to say, clinical trial supply managers do not want to be the individuals responsible for jeopardising or blocking a pharmaceutical's market access.

In striving to secure the smooth supply of clinical trials, professionals will need a thorough awareness of the chain's stumbling blocks as well as the respective strategies to best navigate them. With this in mind, Pharma IQ examines the clinical trial supply pain points and the responding technologies and tactics which have the potential to optimise current clinical trial supply practises.

Distribution Planning And Forecasting Maintaining Costs & The Balance Between Waste And Stock-out

The accurate supply of the product, equipment and documentation required represents one of the biggest challenges to be navigated. The efficient management of clinical supply demands precise planning, forecasting and internal coordination. Conflicting time zones can often hinder fluid communication levels in an international clinical trial. Pharma IQ's 2015 report noted that the majority of small pharma firms were more likely to use excel spreadsheets over professional forecasting systems due to the price points attached to the latter. Participants agreed that poor forecasting had the capability to harm most areas of a clinical trial, primarily drug supply but also cold chain distribution, dosage selection, data analysis strategy, blind studies.

Waste levels within clinical trials can be immensely high due to the level of contingency stock needed, miscalculations and potential stakeholder negligence. Some pharma firms we spoke to stated that based on the medication they packaged around 50% or 60% was never used by any patient and so is destroyed. The waste is at some level attributed to the emergency supply levels needed to be in stock for the entire trial. This excessive supply places wasted resource burden on production facilities. Also, pharma firms need to be aware of any site storage restrictions to avoid capacity complications.

Carsten Jensen, Trial Supply Manager of Novo Nordisk A/S said: "When you have to supply [to] 30 countries, 500 sites - they have medication onsite, some recruit; some never recruit, [others] over recruit, some medication is lost at the local depots. That costs a lot of money. So if you can reduce that [waste] in whatever form, the entire organisation benefits financially from it."
In the case of an adverse event stopping a clinical trial, the sponsor or responsible firm may need to reverse the supply process and return everything to depots for destruction.

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Computer-controlled supply chain management

Automated processes should be implemented to allow for visibility across the supply chain and enhanced control e.g monitoring inventory levels via optimisation technologies to minimise overages.

A recent research study entitled: "Optimising clinical trial supply requirements: simulation of computer-controlled supply chain management" measured

the financial advantages of using computer controlled systems to oversee site inventories.
The simulation found that the computer controlled medication system was more economically beneficial
- The automated version incurred 28% less overage of wasted medication than the traditional method - which ran up a 75% overage.[5]

Visibility through End to end IRT integration

The end-to-end integration of Interactive Response Technology (IRT) through the supply chain will provide pharma firms with global visibility of where all the material is and how it's being managed across all of the countries that are involved in the trial. This can allow for reactive decision making.[2] This visibility could be helpful for simulation and forecasting, managing patient medication, pooling and expiry dating.[4] By positioning product as close to the patients as possible, pharma firms will have the ability to perform a just in time distribution model.

Tool Spotlight

Bio-STARSM from World Courier is inventory management and stock control tool, visibility to stocks per protocol. Notifications are provided on the receipt of a shipment from a site and real time tracking which is required in the implementation of adaptive trials.

Make adjustments to production master plan.

Didier Basseras, Vice President Clinical Supplies - Clinical Supply Chain at Sanofi noted that in regards to the new products coming in for clinical trials most of them are not small but large molecules -Monoclonal antibodies which require some cold chain management. The first step needed here is to adjust the quantity needed for the trial. He explained:"… Obviously regarding what we had in the past with the small molecules, we had huge quantities where we never failed because of manufacturing, because we had always the quantities much more than needed."

"Today, speaking about large molecules and monoclonal antibodies, peptides and so on, the production cycle is pretty long, so we cannot react as we were able to do in the past. We have really to adjust [to] the right quantities. This means that we need close monitoring between the clinical demand and [the] production master plan to adjust the quantities and measure the variance we may have between the clinical demand and the production master plan. [This] is a way to decrease costs."

Simulation technologies

Simulation technologies can be used to inform the integration team on how the clinical trial is performing compared to the baseline and whether the forecast is likely to be met. Simulation softwares can offer different scenarios to assist decision making to see risk levels and spend and resource usage.

Tool Spotlight

N-side's Discrete-Event Stochastic Simulation: A simulation program which presents the aggregated results of multiple simulations to provide more reliable conclusions. A study spanning over a number of years is said to need only minutes to be simulated.

Delay Hotspots

Delays within clinical trial supply cycle times can occur in a number of places for instance due to shipments set-backs, complications at customs due to compliance issues and trade laws, damage to product or equipment during transit. One significant hotspot for delays and added costs is in controlling the temperature of the investigational medicines in both transit and storage and evidencing this with documentation to prove they are safe to use. This highly regulated area is both resource and time consuming. Excursions in temperature cause delays in regards to accessing the details of the deviation, documenting them and then communicating the issue to the sponsor's quality assurance departments so a decision can be made on whether product is still fit for use. Asim Khan, Senior Manager, Clinical Research Pharmacy Services at Amgen LTD notes that this can take from a day to a week of two to complete, a duration of time which can be really inconvenient for the site and patients.

Carsten Jensen, explains: "If you have a hospital in Argentina and you have a patient coming in [one] day - [if] you find you have a temperature deviation you [are unlikely to] get a reply before two or three days. So that patient has to go 100km away from the hospital again, and [return] three days later."

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- **Payload volumetric efficiency** with packaging leveraging innovative techniques and metric calculations to maximise container utilisation.

- **Multi-cell trailers**—refrigerated trailers in which insulated curtains are hung at intervals to create different temperature zones

- **Collaboration** with peer firms on shipments and lanes instead of having vacant space that is wasted due to packaging size constraints.

Stronger Stability budgets

Its advisable to seek stronger stability budgets where possible as to decrease costs of temperature management because verified time out of storage (TOS) can be allocated through the supply chain. Didier Basseras said: "..if we have an ability to manage a product out of refrigeration, this could help to decrease the cost, because from a carrier point of view managing the cold chain is obviously more expensive than just the ambient temperature management. So we have now more requests also to make temperature monitoring also for ambient temperature."

Tool Spotlight

The Quick Stat - Cold Chain Manager monitors the time a package is valid from pack out time, this provides relevant teams with the intelligence to track and intervene if shipment integrity is suspected to be at risk.

COOl CHAIN Labels – CCL Healthcare sticker like labels act as an affordable temperature excursion indicator that changes colour when the relevant temperature threshold has been breached.

"Access to patient" Challenges

The shift towards patient centricity is evident in the clinical trial space, with direct-to-patient shipping models changing how distribution strategies can reach patients and a wider population base. Pharma experts have noted that the closer a site is to a patient's home the more likely they are to join a trial. The direct-to-patient model does require additional considerations for example regarding the temperature controlled transport of the product to the patient. Detailed Instructions on product use for the patient, regular communication with the patient and closely monitored supply chain partners are also needed.

One piece of recent commentary noted that as opposed to investigation sites, pharmacies are more likely to give patients improved access convenience. A known case being the collaboration between Walgreens – which has over 112,000 stores - and Novartis in a clinical trial. Through providing care in pharmacies and using visiting nurses rather than a doctor's surgery significant cost savings can be made.

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Quantified Self devices & Telemedicines

The shift towards patient centricity has triggered the existence of a range of fresh potential monitoring methods, including medical wearables connecting with smart phones and eDiaries.

In a recent whitepaper, Bernard Jaucot, Associate Director Strategic Solutions, Global Clinical Supplies (GCS) at PPD mentioned the possibility of using smartphones and tablet technology to assist drug accountability and traceability. He added that that the potential from smart phones and tablets in the hands of investigators and patients could be: "Incredibly powerful for our business."

One example of the quantified self device with potential benefits for clinical trials is from Alcon and Google's smart eye lens which has capabilities to gather biometric data. These sorts of technologies will become more accessible as technology progresses and could lead to supporting remote clinical trials alongside telemedicine to facilitate virtual visits and real time reporting on adverse events. However, there are inevitable security concerns to consider and regulation restrictions that need to be taken into account.

Tool Spotlight

Tool Spotlight: Remote patient monitoring
Medidata has a cloud solution which fuses connected medical and health devices to paint a holistic view of a patient.

The application of portable devices could work to facilitate remote monitoring of patients in clinical trials, thereby reducing the inconvenience of being involved in a trial as a patient. Also data would be more comprehensive [6]

Hurdling the Stumbling Blocks in Clinical Trial Supply

Labelling Procedures

The formulation of just-in-time labelling strategies, improving labelling standardisation and compliance were highlighted as key areas of interest for 2015 by Pharma IQ's membership base. As clinical trials become more global there is a need in many cases for the special labelling of comparators to enable clinical staff to understand how to handle and manage the drugs. This can add time, financial cost and increase the risk of error of your clinical trial. There are some compliance rulings that block the use of some labelling innovations for example the e-label which would present all the information required on scanning a barcode. Also, the new EU regulation concerning clinical trials has refreshed labelling requirements.

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Simplify the text printed – know the regulations. Carsten Jensen notes that knowing the country specific label requirements can save the company millions. By fully knowing and verifying country specific regulations, sponsors can ensure that unnecessary information is not being printed on labels and within booklets. Sometimes affiliates will state that certain information is needed, but in fact it is not a legal requirement to feature. By simplifying the label or pack type text to state solely what is required has incurred a significant level of cost savings for Carsten. Also, defining a common basic treatment kit and proceeding with the differentiation at the latest stage, should help add agility and flexibility.

Just-in-time Labelling - Just-in-time labelling systems can be used to solve a range of complications for example with pooled studies where labels are finalised last minute or with retest or expiry date labelling after initial labelling has been done. Bernard Jaucot notes that just-in-time labelling systems benefit larger trials with more countries the most - as in general sponsors will see less waste and more importantly have less to produce overall as the overage can be lower.

Comparator Sourcing

The numbers of clinical trials that compare two active drugs, rather than testing a new drug against a placebo, are increasing. A reliable supply of comparator product is required to minimize delays in clinical trials and to ensure reliability of results throughout, by guaranteeing a consistent drug comparison. Any delay to supply increases the risks for the trial sponsor and can be costly. Security of this supply chain is crucial to ensure that no counterfeit comparator is introduced into the trial, which could jeopardize results and not to mention patient safety. There are also more general trade regulations that govern import and export practises that must be adhered to.

Bernard Jaucot notes: "Comparators [are] always an underestimated piece of the budget and can sometimes triple the risk from our perspective as clinical suppliers.

"Look [for comparators] as soon as possible to be sure that they have good batches as well long expiry dates. The other [consideration] is to be sure that [it is] actually still on the market in a lot of countries, we have had that with clients - they discover their comparator is not on the market and [so] need to delay the whole trial."

Didier Basseras added: "The comparative sourcing is for sure one painful point, because when we want to launch a major trial where we want to measure our superiority against the best of the market, obviously speaking about competition, the lab will not help you to fight against their product. It is always difficult to get the product first and second to get the stability data, you have absolutely no help at this point. For instance, when you are getting a drug from the competition, [in] regards [to] the stability data, if it [requires cold chain transport] you have to consider it without any time out of refrigeration."

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Partner with a sourcing specialist: [3]
Of course, a comparator's manufacturer may not want to sell their drug for a comparative trial that may demonstrate superiority over their product. As a purchasing company you may wish to remain anonymous and going directly to the manufacturer reveals identity. Sourcing directly from the manufacturer can be the best way to guarantee a reliable quality and quantity of product for a clinical trial. Sourcing directly from a manufacturer means that drug developers can purchase large, single lots of a drug that has a long shelf life

Many drug developers employ specialist companies with a detailed knowledge of the global landscape to remove the burden of sourcing and supply for comparator trials. These organizations deal with the issues associated with comparator sourcing day in, day out and should therefore find it easier to give options that ensure a reliable and reputable supply.

Globalisation and Country Specific Regulation

A change has been noted in the geographical spread of where clinical trials are taking place, which is expected to continue with emerging markets rising in popularity. [2] This will cause added hurdles to arise with regulations varying in different countries and also general trade regulations which govern import and export measures that must be adhered to. As well as their country specific requirements, emerging markets present logistical challenges with their robust and expansive territories and sometimes sparse infrastructure.

Relevant market players will need to update their conduct in response to the New EU Delegated Act impacting Good Manufacturing Practises for investigational medicinal products for human use. The main changes are said to refer to labelling requirements – for immediate and outer packaging particulars – and will be less flexible than existing requirements. There is no possibility of opting out. References are also made in regards to the cooperation between manufacturers and sponsors. Yet, some specific responsibilities have been removed under shipping requirements. Consultations ended in November 2015 and the results of consultation were released in Q1 of 2016.

Tool Spotlight

Activate –by GoBalto improves operational efficiencies and has 60+ smart standardised country workflows to enable swift study progress. The software gives support on country specific regulations.

For more information on tech and tactics to navigate your supply chain hurdles and to interact with Asim, Didier, Bernard and Carsten attending the 2017 Clinical Trial Supply Conference.

Clinical Trial Supply Europe

23-25 JANUARY, 2017
LONDON,

Pharma-IQ is delighted to announce the return of the MOST interactive and the MOST senior Clinical Trial Supply event, attracting senior clinical supply chain professionals from across the pharmaceutical and biotech industry.

This year's event will continue to look at in an interactive manner how we can effectively manage the supply chain and reduce wastage, with topics of discussion to include: improvements in temperature controlled logistics; forecasting and investigator initiator studies.

New Sessions for 2017

- Applying monitoring technology to minimize temperature excursion
- IRT use for expiry date allocation
- Effectiveness of predictive modelling
- Clinical Trials Supply forecasting and simulation in-house
- Adopting JIT labelling for clinical studies to overcome planning issues for clinical supply
- Challenges faced in complying with GMP when repackaging

Download Agenda

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Resources

1. *http://www.pharma-iq.com/logistics/white-papers/clinical-trial-supply-infographic-facing-clinical*
2. *http://www.pharma-iq.com/logistics/interviews/forecasting-a-brighter-future-for-clinical-trial*
3. *http://www.pharma-iq.com/clinical/articles/the-trials-and-tribulations-of-comparator-sourcing*
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6. *http://blog.mdsol.com/defining-disruptive-innovation-in-clinical-trials/*
7. *http://www.prweb.com/releases/2016/08/prweb13635345.htm*
8. *http://www.centerwatch.com/news-online/2015/05/04/walgreens-leverages-its-100-million-customer-database-in-patient-recruitment-deal-with-five-big-pharma-companies/*