Clinical Trial Material Storage and Distribution – A Critical Mission

Introduction
Manufacturing investigational medicinal products (IMPs) and ancillary supplies is a complex process, and it is subject to change at every stage. There is much at stake for both sponsors and clinical research organisations (CROs), from being responsible for IMPs that represent millions of dollars in investment to the health of patients involved in the trials. As if manufacturing of IMPs wasn’t challenging enough, the appropriate storage and distribution of such sensitive products can be an adventurous journey in itself if not carefully planned and managed. Is there one solution that fits all situations? Certainly not.

Clinical supply managers must evaluate many things during planning stages. For example, what is more important? The time to delivery or the quality of transport and product integrity until administered to a patient?

It is important to understand key storage and distribution strategies such as central depot, the direct-to-site shipment approach, as well as mixed alternatives combining central and local depots. There isn’t a one-size-fits-all solution. Therefore, it is important to evaluate the pros and cons to identify the optimal individual study approach. Since storage typically does not end at a depot, it must also be assured that materials are stored safely at sites and even with patients who are participating in clinical trials.

A holistic view of storage, distribution and handling of deviations is essential for optimising costs and ensuring safety of products and patients. Equally important is a distribution plan that reflects product stability and requirements of the involved countries.

Defining the Clinical Trial Material Supply Chain Strategy
An annual PAREXEL Clinical Logistics Industry Survey of Biopharmaceutical R&D Supply Chain Leaders, conducted by ISR in fall 2013, found that the top three risks identified in the supply chain were product integrity, concern around supply chain disruptions, and fear of not meeting timelines.

Typically during the planning phase, project leaders need to clarify essential questions to prepare for the successful storage and distribution of all clinical trial materials at any time. Certain parameters must be identified upfront to plan a high quality storage and distribution strategy. These should include: total number of investigational sites and patients; planned country distribution of sites and patients; product stability data and shelf-life; available product quantity; frequency of administration; storage conditions; (e.g. controlled ambient 15-25°C); controlled/uncontrolled substance; cost of drugs; study length and planned enrolments.

Sophisticated forecasting and software-aided simulations can enable supply chain managers to assess some of these key questions, including the quantity of medication required, minimum requirement to launch a study, the best size and types of medication packs to produce, and the choice of central/local depots for efficient IMP usage and supply.

If, for instance, product manufacturing is highly cost-intensive, temperature-sensitive, and has a short shelf-life, the supply chain solution may differ from a product that is temperature-sensitive but less expensive to produce. In the first case, the best strategy would be frequent shipments from a depot to the site, whereas in the latter, a much higher average of products may be manufactured and higher quantities distributed to sites per shipment.

Country distribution also requires significant upfront planning. For example, while treatment-naïve patient populations in emerging drug markets are attractive for trial recruitment, it may take longer for trial approval by local authorities, and the local infrastructure for storage and distribution can be challenging. Further, importing a drug may require specific customs processes and additional tax may be needed, increasing the supply chain cost drastically. It is therefore essential to work as close as possible with clinical teams to balance faster recruitment of patients to minimise total expected project cost.

Ensuring Quality – Knowing Your Partners
In addition to planning ahead, clinical supply chain managers must also develop close relationships with reliable business partners. Each and every supplier who participates in storing and distributing IMPs and non-investigational medicinal products (N-IMP) must be qualified and able and willing to follow good manufacturing practices (GMP) requirements. Even those involved in direct distribution, namely couriers, should follow standards such as the EU GDP guidelines.

To ensure suppliers are reliable, a three-step qualification with each party is recommended, starting with an RFI approach to obtaining business and quality feedback. Step two should involve a supplier audit, followed by implementing quality-technical agreements in addition to standard business terms and conditions.

CROS and CMOS must also be aware of storage capabilities at investigational sites. During study planning, sites need to be assessed in terms of their respective storage space. For example, it is important to evaluate upfront whether or not key cold chain aspects in case products must be stored in controlled temperature areas. If so, validated cold chambers/refrigerators must be available as a prerequisite. Often this is not the case. Appropriate temperature loggers, even refrigerators on occasion, will need to be distributed alongside the drugs to guarantee 365/24 environmental monitoring.

While managing sites is complex, the process can be even more challenging for clinical supply managers who need to deliver directly to patients as part of the growing trend of direct home delivery. However, some of the same principles used to manage sites can be used in these situations.
Cold Chain Considerations
To ensure patient safety and uninterrupted dosing schedules throughout the study, distribution facilities and managers need to ensure real-time supply chain metrics. Facilities also must support controlled temperature storage at various temperature levels such as ambient, controlled ambient, refrigerated, frozen and deep frozen.

The cold chain is a critical part of the biopharmaceutical mix. Imperative for ensuring product safety and stability – and therefore product safety – a correctly managed procedure is high on the agenda. While this is true for commercial medicines, the issue is particularly crucial with clinical trial materials.

The majority of today’s IMPs require temperature control, especially in the realm of oncology and large-molecule research. This is not simply a matter of inserting a few gel packs: clinical supply managers must ensure that they are transported in ambient conditions (typically around 2–8°C), making use of tools such as temperature monitoring devices, temperature-controlled shipping containers and full track and trace technology.

To ensure proper temperature and monitoring, a computerised environmental (temperature and humidity) monitoring system should be used in addition to internal and external security systems.

User-friendly web interface systems and real-time data exchange between third-party and client systems is another key aspect for proper storage practice. Real-time data allows companies to make decisions throughout the process, accelerating time to market and reducing costs.

Regulation Preparedness
The ultimate aim is clear. Whatever hurdles are faced en route – language barriers, climate changes, complex import and export procedures – the IMPs are required to finish their journey in the same condition as when they began. This requires CROs and CMOs to have a strong understanding of regulatory requirements at a global and local level, as well as accounting for the impact of timeline as it relates to cold chain management.

Checklist for clinical supply managers:
- Quality system (fully documented, change control system, CAPA in place).
- Management of outsourced activities.
- Quality risk management.

Correct distribution of medicinal product relies upon:
- Premises.
- Proper cleaning and maintenance programme in place.
- Temperature and environmental control – suitable equipment and procedures in place to check and monitor the environment.
- Initial temperature mapping; then monitoring equipment installed.

Equipment
- Designed, located and maintained to a standard that suits its intended purpose.
- Monitoring should be calibrated at defined intervals based on a risk and reliability assessment, including alarms when excursions from predefined storage conditions.

- Repair, maintenance and calibration exercises should not impair medicinal products.
- Validated computerised systems to ensure ability to achieve desired results, accurately and consistently.
- Qualification and validation – scope of which must be determined and should include install qualification, operational qualification and performance qualification.
- Documentation: Written procedure.
- Instructions.
- Contracts.
- Records and data, in paper or in electronic form. Longevity of at least five years; and include at least name of product, date, quantity received, supplied or brokered, name and address of supplier (etc.), batch number.

Operations:
- Identity of medicinal product is not lost, and is distributed in accordance with information on the outer packaging.
- All medicinal product distributed in the EU must be released in accordance with Annex 13 by a qualified person (“QP”).
- Qualification of suppliers (should be controlled by procedure). Verify that supplier complies with principles and guidelines of GDP.

Qualification:
- Qualification of customers.
- Ensure holder of wholesale distribution authorisation.
- Receipt of medicinal products.
- Ensure arriving consignment is correct.
- Medicinal products requiring special storage or security should be prioritized.

Storage:
- Separately from other products which may alter their content.
- According to storage conditions.
- To prevent breakage, spillage and contamination.
- Material approaching or beyond their expiry date should be withdrawn from available inventory.
- Destruction of obsolete goods.
- Appropriately identified and removed from inventory.
- Records maintained.

Order Fulfilment and Export:
- Controls in place.
- Document (bill of materials, delivery note, etc.) stating pertinent information (batch number, product, protocol, consignee, quantity, safety features, etc.).
- Complaints, returns, recalls, suspected falsification and returns:
  - Complaints - recorded with all details and CAPA established.
  - Returns handled according to written procedures and conducted in accordance with national law.
  - Falsified medicinal products – inform competent authority of any material suspected in accordance with written procedures.
  - Recalls – handled in accordance to written procedures, and should be capable of being initiated promptly.
Track and Trace

Of course, arguably one of the most important aspects of storage and distribution for clinical supply managers is keeping track of products. Fortunately, technical systems and applications in the clinical trial material supply chain can help manage the inventory with a full track and trace of the IMP and N-IMP.

There are many rules and regulations associated with how IMPs are tracked. For example, the European Commission DG Health & Consumers have set clear expectations in the EU-GMP Chapter 8 on Complaints, Quality Defects and Product Recalls. Specifically, according to chapter 8.24, in the case of IMP, all trial sites should be identified and countries of destination should be indicated. Further, in the case of an IMP for which a marketing authorisation has been issued, the IMP manufacturer should, in cooperation with the sponsor, inform the marketing authorisation holder of any quality defect that could be related to the authorised medicinal product. The sponsor should implement a procedure for the rapid unbinding of blinded products, when necessary for a prompt recall. The sponsor should ensure that the procedure disclosed the identity of the blinded product only in so far as is necessary.

Technical systems should manage inventory of trial drugs at manufacturer, central depot, local depot, during transit, at investigational sites and ideally also with patients participating in clinical trials. During a recall, the products must be immediately quarantined at any storage locations, and all involved parties must be informed and a solid recall process enacted.

When temperature-sensitive drugs are distributed from a central depot to a local depot, both the shipment and temperature need to be monitored. Upon arrival at final destination, temperature read-outs from embedded data logger sensors have to be performed, and the drug can only be released for further usage upon analysis of results. The same applies for a distribution from local depots to a site or direct to patient. Courier providers must be trained on drug-handling procedures, as must sites and patients.

The industry has developed track and trace solutions, mainly IRTs – interactive response technologies - often combined with randomisation functionality. Many of these systems do not focus on the complete supply chain (central depot, local depot, courier, broker, site and patient) and do not have full traceability, for instance not what is managed and maintained within a central/local depot. For instance, what if a product at a depot was outside the temperature for a small time-frame – in line with stability data? It could still be usable for the trial if no further temperature extensions were documented. However, how would all temperature data be mapped?

Therefore, CMO track and trace systems and IRT solutions need to be further interfaced to secure end-to-end supply track and trace.

What if there is no IRT solution in place, as the study is an open label trial? In addition, what should be considered regarding additional clinical trial materials needed for the site, such as an Infusion pump and specific application material? Still inventory control and track and trace are key tools to help ensure uninterrupted outbound supply, and it is also a vital tool in recall situations.

Ideally, organisations handling the supplies should have a system in place to manage the journey of such products from depot to site.

Graph 1 shows an example of a specific web-based validated supplies order module to manage such mission-critical track and trace.

Future Considerations

As mentioned, there is no one-size-fits-all solution for storage and distribution, and what might be essential in one trial might not be the most important consideration in another. There are, however, universal best practices that CROs and CMOs can employ to make storage and distribution easier to implement: plan ahead, know your partners, be knowledgeable about the opportunities you will face (i.e. the cold chain, local regulations) and leverage available technical tools to the fullest extent possible.

The logistics of dealing with effective storage, distribution and regulatory compliance can be a complex and complicated process. However, by following established best practices, you'll ultimately help simplify the drug development journey through the clinical trial process, and even more importantly, the outcome of the trial will remain intact.