CLINICAL LOGISTICS – MEETING THE 21ST CENTURY CURES CHALLENGE

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Numerous changes in the pharmaceutical industry have affected the nature of clinical trials, which in turn have led to the evolution of systems used for the supply of clinical trial materials.

Today, both large biopharmaceutical companies and emerging pharma/biotech firms rely on clinical logistics organizations (CLOs) to ensure the seamless flow of shipments and information, and reduce waste and inefficiencies in the global supply chain. With the rise of evidence-based medicine and a patient-centric industry focus, however, improving efficiencies is no longer sufficient. Successful CLOs must employ state-of-the-art information, inventory, temperature control and other technological systems to provide patient-focused delivery of clinical trial materials to any location in the world, on time and within specifications.

INCREASE IN GLOBAL CLINICAL TRIALS

Efficient clinical trial supply has simultaneously become increasingly important and challenging in recent years. First, there are simply many more trials being conducted – according to the National Institutes of Health, the number has increased 33-fold since 2000.[1] The complexity of clinical trials has also increased dramatically. Most are now global, multi-site studies with locations in less- and poorly developed regions. In some cases the size is needed to achieve sufficient patient enrollment. In others – particularly for orphan drugs, which are a growing percentage of the pharma pipeline – there is a need to evaluate efficacy and safety in specific and very limited patient populations, and access to patients across the globe is necessary.

Clinical trials also often last much longer in order to demonstrate improved efficacy over existing therapies (a key performance metric in the age of evidence-based medicine) or demonstrate the long-term safety of treatments designed for chronic diseases.[2] Trial protocols tend to be more complicated as well, and many involve complex dosing schedules. The use of adaptive trial designs, in which trial parameters may change in response to early trials results, adds additional complexity. The percentage of candidates that are biologically derived has also increased significantly. Most biopharmaceuticals are temperature-sensitive and require shipment in insulated packaging designed to maintain them at low temperatures. In many cases, administration of such drugs is also complex.

These changes have not only led to dramatic increases in clinical trial costs, they have also posed many challenges with regard to effective clinical trial design, the management of massive quantities of generated data, and the timely supply of on-spec clinical trial materials. Most sponsor companies have responded by outsourcing the vast majority of their clinical trial activities to specialist providers that offer increased efficiencies and reduced costs. For the supply of clinical trial materials, clinical logistics organizations (CLOs) are relied upon to ensure the seamless flow of shipments and information and reduce waste and inefficiencies in the supply chain, despite increasing and varied customs regulations.

Until recently, the improved distribution models provided by CLOs have been sufficient to meet the needs of pharmaceutical clients. As the industry becomes more patient-centric, however, even these more advanced, centralized clinical trial supply chains must evolve.

EXISTING SYSTEMS HAVE MANY ADVANTAGES

Supply chains managed by third- and fourth-party clinical logistics organizations that use interactive response technology (IRT) and other advanced IT systems are far more efficient. Specific quantities of needed doses are provided, rather than large quantities of all possible doses, and patient-specific labeling is no longer required. Both changes have significantly reduced medication waste, which has become increasingly important, as the costs of drugs have skyrocketed. Inventory is now stored in central, regional locations (depots) and shipped as needed in small

quantities with general country labeling; sponsor companies need only supply the CLO.

For instance, in Europe, one depot with an EU Qualified Person can in some cases serve the entire region. There are, however, several countries in Europe with significant import challenges, such as Russia, Ukraine, and Belarus. Therefore, the use of one vs. several depots in Europe varies depending on the specific drug product (its value, stability/sensitivity), the comparator drug, the therapeutic indication, the number of patients/patient visits, and the trial phase. Regional depots are also effective for serving emerging clinical trial markets.

This approach has also helped overcome the challenges of burgeoning and evolving import regulations and requirements across the world. Customs and trade experts located at each hub are able to ensure compliance and allow the sponsor to avoid the need to obtain import licenses for every country. CLOs can advise clients on the value of the drug and estimate taxes and duties, plus offer study-specific 4PL services with reduced numbers of shipments to each investigator site, through consolidation of all of the different materials needed for clinical trials at that site.

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As IT and communications technologies have advanced, CLOs have also been able to further increase the efficiency of their operations and increase their ability to track and manage supply chain data. This improved supply chain intelligence has, in turn, led to further improvements in CLO services, including increased optimization of material deliveries (quantities and timeliness) and greater reduction of costs. In some cases, they have also enabled more complex clinical trial protocols through the on-time delivery of sensitive clinical trial materials.

The latest Sentry technology from Marken, for instance, allows online GPS tracking, in addition to monitoring of temperature, vibration, light, and shock exposure. Automatic text messages can be sent to the final destination when the delivery is 10 miles away. This "Amazon-like" experience responds to the increasing expectations of both patients and sponsor companies. Importantly, all shipments must be fully compliant with the increasingly stringent regulations and guidelines of each country, while also providing these advanced tracking features.

AND PATIENTS ARE TAKING CENTER STAGE

With the advent of the Internet and social media, potential trial participants, including both patients and healthy volunteers, are far more educated about diseases and potential treatments, as well as the possible risks presented by clinical studies. They also share information and seek advice from advocacy groups through various online forums, websites, and blogs. Consequently, participants are in a position today to change current perspectives about clinical trials.[3]

Indeed, clinical studies are only successful if sufficient numbers of patients are enrolled, follow trial protocols, and remain active participants. The greater awareness of patient populations has led many pharmaceutical companies to realize that clinical trial participants should not be considered only as subjects, but as key collaborators in the clinical trial process.[4] The concept of patient-centric trials is, as a result, becoming a reality.

Considering patient preferences and needs during trial design can lead to the development of trial protocols that are easier and more convenient for patients to follow, which leads to greater patient adherence and retention, and thus more reliable trial results. Consideration of both patient and caregiver capabilities, schedules and locations, as well as patient comfort, is important.

The interest of many patients in the latest personal electronics technologies can also be leveraged to facilitate trial participation and better data collection. Smart watches, fitness trackers, and other wearable devices on the market today can be used to track and transmit real-time patient data, while also providing trial managers a means for communicating directly with patients on an ongoing basis. Smartphones, too, are easily accessible, non-intrusive tools that can make it easier for patients to regularly log data and increase the likelihood of participation throughout long-term trials.

WHY THAT MATTERS TO CLOs

One consequence of the move towards patient-centric trials is increased expectations for direct-to-patient delivery of trial materials, patient home treatment, and the capture of multiple clinical and biological data points at patient homes. Such an approach can actually lead to more successful patient recruitment and, significantly, increased patient retention, because people are more willing to participate in trials with this type of personalized service. In addition, direct-to-patient clinical trial material delivery increases protocol compliance and the likelihood of patient retention throughout the extent of the trial.

It can be challenging, however, as delivery to many different residences is often required. In addition, coordination with nurses or other caregivers may be necessary if special delivery systems, such as injection and infusion, must be used.

It is also worth noting that direct-to-patient clinical trial material delivery can be very effective for clinical

trials designed to evaluate orphan drugs, indications for patients that are dependent on a legal representative or family members (certain CNS and oncology indications) and pediatric trials. In many cases, because it is difficult to locate patients with rare diseases, orphan-drug programs often have long-term trials. Under these conditions, the line between clinical trials and prescribed-drug delivery to patients is somewhat blurred. Getting the clinical trial materials to these patients can be critical to the success of such programs.

NEXT-GENERATION MEDICINES ARE IMPORTANT TOO

The number of clinical trials for the evaluation of next-generation treatments includes cell and gene therapies, which is increasing rapidly. These clinical trials pose significant challenges with respect to delivery of clinical trial materials. First, gene- and cell-based bio-hazardous materials require special handling under cryogenic conditions (liquid nitrogen storage), which is not yet widely available on a global scale. Second, samples taken from patients must typically reach the manufacturing site within 28 hours of the patient visit. Once the drug is prepared, it must then be delivered back to the specific patient for treatment, also within a short period of time.

The development of innovative, specialized technologies is also crucial if CLOs and others involved in clinical trial design and management are to facilitate sample preparation; transport across country borders, delivery within short timeframes to the manufacturing site for patient-specific drug product preparation, and final delivery back to the patient for treatment is a complex undertaking. It is made more challenging by the fact that the regulations for handling such shipments can vary from country to country, and therefore specialized knowledge and skills are required. As these therapies move through the pipeline and approval process, it is even more important to design clinical supply chains with the needs of commercial products in mind; supply chains for marketed drugs will continue to be critical and increase in complexity.

Advanced technology is the solution to meet the increasingly complex needs of the sector while simultaneously increasing study efficiency and reducing cost. Indeed, many of the achievements in clinical logistics can be attributed to advances in information technology. Cloud-based systems for electronic data capture (EDC) are now employed for shipment tracking and clinical trial data collection, monitoring, and reporting. Such real-time data management tools allow ongoing data analysis and transparency into the supply chain, even with regards to the physical conditions of individual shipments.

While increasing the efficiency of the regulatory review process is recognized as a key requirement for accelerating drug development, such improvements will be slow in coming. More immediate solutions must also be taken in the meantime. Researchers in one study noted that the use of lower-cost facilities and in-home testing (which would be facilitated by direct-to-patient material delivery and home treatment) and increased use of mobile technologies and EDC.[2]

The FDA is, in fact, committed to the use of advanced technologies to address rising drug development costs. In 2010, then-Acting Director for the U.S. Food and Drug Administration's Office of Critical Path Programs, Dr. Leonard Sacks, noted that "Harnessing information technology and novel scientific tools in the service of medical product development has been a central priority for FDA. These innovative tools provide a historic opportunity to move medical product development into the 21st century and to deal with the challenges of spiraling research and development costs in the face of diminishing returns."[5]

The U.S. Congress is also focused on the need to accelerate the discovery, development, and delivery of promising new treatments and cures for patients. In June 2015, the U.S. House of Representatives passed the 21st Century Cures Act, a bipartisan piece of legislation targeting multiple areas for improvement.[6] Not surprisingly, one of the five key issues identified in the Act is the need to streamline clinical trials through greater adoption of adaptive clinical trial designs and the use of innovative technologies and statistical modeling. P

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