



Adapting to a Changing Environment

Steve Giampapa and Rognvald Lamb of Fisher Clinical Services discuss the need to find new strategies for managing a global network

Image: Fisher Clinical Services

At no time before have the challenges of conducting international clinical trials – or the stakes involved – been greater thanks to the changing geography and focus of drug development today. Two key trends – the migration of studies to new corners of the globe and accelerating investment in biologics – are stretching the capabilities of global networks. This article will examine how global networks are adapting to these new circumstances and will offer some prescriptions for maximising network performance in an environment of rapid-fire change.

GLOBAL QUALITY STANDARDS TAKE HOLD

Clinical trials have grown larger, longer, costlier and more complex, and are migrating further afield to countries that rarely took part in studies 20 years ago. One result is that consistent global quality standards are supplanting local standards in Asian, eastern European and South American countries where trials recently began taking place.

Pharmaceutical sponsors seeking cost-savings and rapid patient recruitment have made China, India, Singapore, Taiwan, Russia, the Czech Republic, Poland, Hungary, Israel, Brazil, Argentina and South Africa top choices for clinical trials, alongside more conventional choices like the US, UK, Germany and Ireland. Today, about 40 per cent of trials take place ‘offshore’, projected to increase to 65 per cent in the next few years (1-3).

As time goes on, other countries – among them Costa Rica, Chile, Peru, Colombia, Belarus, Ukraine, Georgia, Moldova, Slovenia, Romania, Kazakhstan and Turkey – have been joining the clinical development fold. Even Japan, which has traditionally been one of the most difficult markets in which to conduct clinical trials, is increasingly becoming a sought-after location for studies (1-3).

In addition to permitting the study of drugs in many different ethnic groups, the inclusion of additional countries as clinical trial sites has facilitated the adoption of global quality standards and



Standard Operating Procedures (SOPs) across global networks. Good Manufacturing Practice (GMP) compliance to global quality standards is now enforced consistently, regardless of whether a trial is taking place in Brazil, Belgium or Belarus, replacing generally less stringent local requirements of the past.

SPECIAL HANDLING REQUIRED: BIOLOGICS DRIVE COMPLEXITY

Aside from the addition of countries where trials are now taking place for the first time, the most significant impact on global networks has been double-digit growth in the number of studies involving temperature-sensitive biologics.

Biologics, which must be shipped and stored in the cold chain at controlled temperatures, are also the biggest transport management challenge for global networks because loss of temperature control requires replacement of costly product.

Development costs for biologics, frequently valued at \$1,000 to \$2,000 per dose, exceed those of the average small-molecule drug by about \$400 million. The high, per-dose price makes it imperative to minimise loss or waste – a particular challenge considering that a lack of stability data in early development means that biologics' shelf lives are frequently unknown and product could fall out of specification during the course of a trial (1,2).

The extra effort is well worth it from a sponsor's perspective. Sixty per cent of revenue growth for pharmaceutical companies moving forward is projected to come from biologics, which are large-molecule, protein-based therapeutic agents, including therapeutic proteins and monoclonal antibodies.

Temperature control requirements make the handling of biologics a cumbersome process requiring formidable layers of oversight and meticulous packaging, as well as special transportation considerations. The recent surge in biologics testing has also prompted a tightening of regulations around temperature control and monitoring, especially concerning bulk shipments to depots.

A common error with respect to biologics is the inadvertent failure to declare a product as a biologic and consequently failing to package it properly. Inadequate packaging can lead to temperature excursions and product that goes out of temperature range for a period of time must be replaced. That's why ensuring personnel are trained in proper shipping and receiving processes for temperature-sensitive materials is important. Double-checking supplier declarations is another good rule of thumb.

Efforts to prevent temperature excursions are driving the adoption of new, technically sophisticated packaging solutions. Specialised packaging that includes insulation and refrigerant offers greater protection for temperature-sensitive product but is more expensive and generally not reusable. Sponsors worried about having to replace potentially hundreds of thousands of dollars worth of biologics frequently opt to pay higher handling costs in exchange for an extra margin of security (4).

Complying with Good Distribution Practice (GDP) during the movement of product is also mandatory for ensuring that material integrity and efficacy are not compromised. Supply chain managers are always seeking better ways to maintain and monitor

the temperature of materials in transit. Shipping containers featuring a combination of both cooling and heating mechanisms are increasing in use, for example.

Another potential transportation solution is the use of radio frequency identification (RFID) transmitters to continuously monitor the temperature of product in transit, offering a significant advantage over traditional monitoring. Deployment of RFID equipment throughout the supply chain is needed since RFID can alert supply chain managers if a product is going out of temperature range. Unfortunately, RFID has no mechanism for preventing failure and must be switched off while on an airplane. Global positioning system (GPS) technology is also being explored.

Packaging and monitoring aside, there are other shipping challenges with respect to biologics. Because some biologics are designated as hazardous materials under UN shipping regulations, they may be subject to flight restrictions. Some airlines, for example, prohibit transport of biologics on passenger flights; others do not permit biologics in cargo holds containing live animals.

INDISPENSIBLE: A KNOWLEDGEABLE GLOBAL TEAM

Given such complexities, it stands to reason that the effectiveness of a global network is, by definition, dependent upon the quality of its team. Experience, in-country knowledge and relationships, and seamless communication are indispensable.

In addition to experience and a high level of knowledge, effective global teams must have access to information tools that enable them to stay on top of the complex tiers of policies, regulations, and other information governing the movement of clinical trial supplies across the world.

The most valuable tool in the team's arsenal is a central database that serves as a repository of globally sourced information. The database contains detailed information about import/export, tax and duty regulations, customs requirements, third-party facilities and collaborators, and preferred air and ground transport carriers.

The database is the go-to source for answers to questions about, for instance, Turkey's recent changes in qualifications on export procedures, the preferred airlines for shipping materials to Russia, and whether premium ground transportation is recommended in Romania. It goes without saying that frequent updates are necessary in order for the database to remain up-to-date on complex, ever-changing regulations, particularly in emerging markets.

MANAGING CUSTOMS ISSUES TO PROTECT PRODUCT VIABILITY

Aside from the threat of temperature excursion during, say, the 11-hour flight from Allentown, Pennsylvania to Cape Town, drugs could similarly perish on the tarmac should a customs official take issue with product declarations and delay clearance for five days. In the end, most customs issues boil down to three causes: incomplete or inaccurate documentation, bureaucratic procedures or inexperience. In countries where clinical trials are being conducted for the first time it can be a combination of all three.

Incomplete or inaccurate declarations, particularly with respect to valuation, can result in prolonged customs delays. Resourceful customs officials, who believe that drug shipments are undervalued, are increasingly turning to online drug prices as a basis for revaluing commonly used drugs. In some emerging markets, customs officials may also inflate the valuation of study drugs as a means of generating revenue.

In highly bureaucratic countries, jurisdictional disputes, such as a refusal by regional authorities to recognise drug import licenses issued by national authorities, are all too common. Customs officials in such countries are often solely focused on matching numbers and counting packages instead of ensuring the on-time and safe importation of drugs.

Finally, customs delays may also occur in countries where there has been a recent rise in the number of clinical trials simply because inexperienced customs officials are unfamiliar with proper importation regulations.

An effective strategy for managing the often time-consuming customs process is use of a premium courier company with a strong local presence. In one recent example, customs officials in a country where trials are beginning to take place did not recognise an import license issued by the country's Ministry of Health. Fortunately, the representative of a premium courier company was on site, and able to assist in expediting matters by tapping local knowledge and contacts and diplomatically guiding customs officials. The product was soon on its way to the local network depot.

In some countries, it may be necessary to strike a balance between adhering to customs requirements and preserving the integrity of a trial. Taiwan, for example, demands that all trial drugs be declared, even those earmarked for blinded studies. While such information is necessary in order to clear Taiwanese customs, it is important to remove it before materials are delivered to clinical sites or the study blind could be broken.

ON-THE-GROUND LOGISTICS: BALANCING RISK AND COST

Ground handling upon arrival is a highly vulnerable point in the clinical supply chain, especially with respect to temperature-controlled materials. That's why a thoughtful analysis of risk and cost, rather than a broad-brush approach, should drive decisions about materials distribution and storage.

The choice of a standard, as opposed to a premium or speciality, courier or freight company should be based on countries, sites, materials being shipped and timing. Use of a premium carrier is unnecessary if a delivery is not temperature- or time-sensitive.

Instead of opting to use only standard or premium couriers, a so-called 'mix-and-match' approach to global coverage is an effective strategy. Courier decisions are made on a case-by-case basis, leveraging knowledge and experience with individual markets and sites.

A standard courier is an appropriate choice for shipping materials within North America, western Europe, or to countries with established standard processes. For other destinations, a premium courier may be a better choice. An example of a country in which a premium courier should be used is Romania, which is easily accessible by flights into Bucharest. However, clinical supplies unloaded in the capital must sometimes then be

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transported to remote areas of the country – a journey of up to 72 hours. Argentina, Brazil and Slovenia are other examples of countries where premium couriers are preferred.

Network-owned and operated facilities for receiving, packaging, storing and distributing clinical trial materials are preferred to subcontracted facilities. In addition to GMP-compliant packaging and distribution, desirable facilities feature a common IT infrastructure that provides continuous visibility and a project management team with local knowledge and relationships at each location. The value of such integrated facilities in countries and regions where a high volume of clinical trials are underway, such as China, India and Russia, cannot be understated.

INTO THE FUTURE

As we near the end of the decade in which emerging markets came into their own as clinical trial sites and sponsors began investing heavily in biologics, global networks have grown in size, role and stature to become full partners in the development process. It is only by providing sponsors with a consistently high degree of control, compliance and transparency that global networks will continue to be a vital link in the supply chain.

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