CT Supply Chain Management

The key challenge clinical trial supply chain (CTSC) managers face in global distribution is ensuring that supplies arrive at the trial sites on time and in good condition. Effective distribution requires a knowledge of regulations in the country of origin and trial countries, qualified suppliers and storage infrastructure, and control of supply temperature and conditions for the duration of delivery.

Regulatory compliance

Regulatory support is a critical aspect of clinical trial supply distribution, requiring the creation and control of essential documents, study initiation, and activities to ensure a seamless supply of clinical materials. Another regulatory role is labeling management, ensuring adherence to the labeling requirements of different countries, and managing the translation of it.

When exporting clinical materials, CTSC managers must first ensure regulatory compliance with many government agencies in both the originator and destination countries.

In the United States, clearance is required from agencies such as the Food and Drug Administration, Department of Commerce, Department of Homeland Security, and Drug Enforcement Administration (DEA), as well as state agencies to ensure that materials are allowed to be delivered to destination countries, vendors, companies, and individuals, and that they are not on one of the many government controlled sanction lists or embargo lists.

DEA-regulated supplies require additional clearances in the United States and abroad. Industry-specific computer software is available to facilitate many of these functions.

Companies must also be knowledgeable about International Air Transport Association (IATA; www.iata.org/index.htm [5]) regulations, which include guidelines for packaging and labeling diagnostic specimens. For example, shipments to Europe can be made to one country

within the EU and can then be freely circulated within the EU, subject to some minor exceptions. The UK is commonly used as the EU port of entry since its importation requirements are often the least stringent.

All investigational supplies manufactured outside of the EU must be released by a registered Qualified Person (QP) for use in European clinical trials. The QP is responsible for the compliance of imported supplies with European cGMP regulations and guidelines.

Critical Forethought for Global Distribution

TOPIC	CRITICAL ISSUES
Regulatory compliance	Compliance with origin and trial country requirements, IATA and labeling regulations QP release of EU imports
Shipping and logistics	Freight carriers, storage conditions, country/port of entry, regulatory requirements
Depots	Country differences, when advantageous, cost/risk assessment, unused supply recov
Supply management	Benefits of advanced technology, that is, IVRS versus the costs. Is real time informatic important?
Material stability	Management of time- and temperature-sensitive supplies, ambient shipments, cold-chain distribution
Comparator sourcing	Ensure product is genuine, preferred lot availability, expiration dates, pricing. Would globally equivalent product be beneficial?

Source: Lis, Gourley, Wilson, and Page.

Table 1. Companies must perform considerable preliminary work to ensure regulatory compliance since noncompliance by just one of their subsidiaries could jeopardize the corporation's import/export privileges.

Critical Forethought for Global Distribution

Depending on the destination, the particular clinical trials materials, and how they need to be handled, global distribution requires considerable preliminary work (see Table 1). Initially, the company must obtain import/export permits and other documentation in compliance with the requirements of each country.

The CTSC manager should thoroughly review documentation to make certain it is accurate and complete. Every country has its own unique terms, procedures, requirements, interpretations, and penalties, and each must be addressed individually. The risk of noncompliance by even one company subsidiary can potentially jeopardize the import/export privileges of the entire corporation.

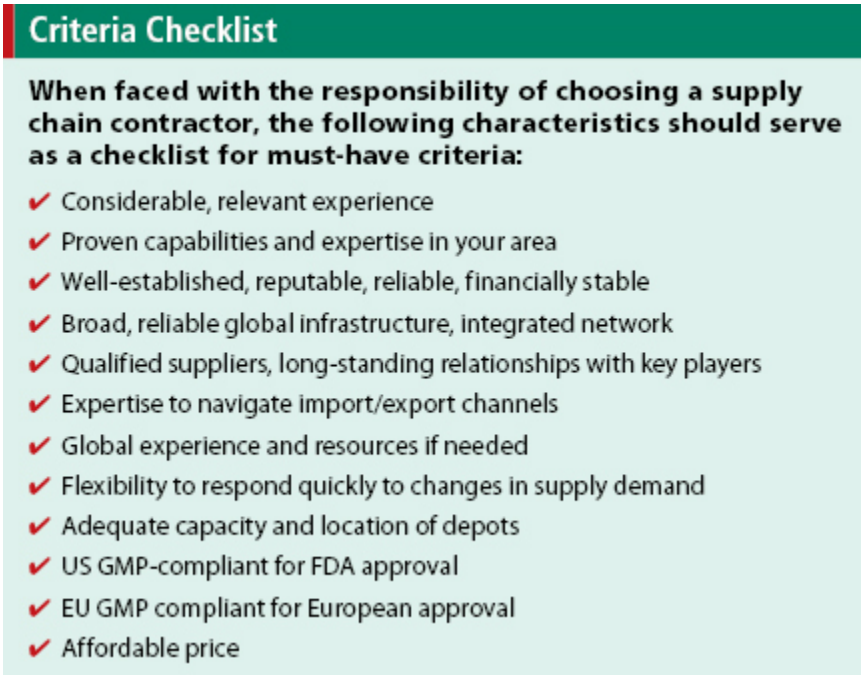
Shipping and logistics

Experienced CTSC managers and contractors have an established transportation and storage infrastructure, including vetted third-party freight carriers and storage facilities, for efficient delivery. With a solid knowledge of shipping options and current regulatory requirements, they determine the optimal distribution logistics:

- What are the most effective routes of transportation?
- Who are the most efficient, reliable freight couriers?
- Which freight courier is best for a particular shipment?
- What is the best way to coordinate shipping schedules and manage requirements for air, ocean, and ground transit?
- Which port of entry has the most efficient government customs clearance process?
- What special arrangements must be made for time-and temperature-sensitive supplies?

Distribution managers should also be knowledgeable about the unique regulatory requirements of each country.

China, for example, requires companies to make entry arrangements with a Chinese corporation that has a relationship with the Chinese government. Otherwise, the supply may be delayed or the company may need to use a freight forwarder with a Class A license. In India, the commercial invoice is stamped and becomes the import permit. For Israel, a pro forma invoice detailing materials, use, and estimated cost is required for appropriate taxing. A common problem with less experienced supply chain managers is the arrival of a shipment without all the required documentation. This can result in weeks-long delays at the airport or depot, which can compromise the trial timeline



Criteria Checklist

and cause spoilage of temperature sensitive supplies. If there is an extension or delay to the trial, and if supplies were manufactured before stability data was available, expiration dates can also be a problem.

Depots

For large global studies, depots are often an integral part of delivering supplies in a timely, cost-effective manner.

Depots should be prequalified, GMP-compliant clinical drug storage facilities with controlled room temperature and cold-chain storage. Often depots are established in areas where there are lengthy customs clearance and import license application processes, complex import requirements, and long shipment times due to distance.

In countries such as Canada, for example, depot delivery is unnecessary, as the domestic delivery system is similar to that in the United States and there are simplified customs procedures between the two countries. But in other countries, such as Argentina, Russia, China, and India, a depot is preferable because of sheer distance, and these countries require considerable time to clear materials.

Depots are also advantageous when supplies are required on-site within a short time of order, when there are large numbers of patients and sites in one area, and for reducing the risk and cost of cold storage shipments.

Costs are another important factor in determining when to use a depot, considering that it is far less costly to deliver one or two bulk shipments to a depot than repeated shipments directly to sites. There is also increased risk with repeated shipments. Depots can arrange the distribution to study sites through local country affiliates.

When choosing a depot, find out if it has the capability to recover unused supply from the site and ship it back, if necessary. If unused supply should be destroyed, determine the chain of custody.

Supply management

Investing in new technology, such as Interactive Voice Response Systems (IVRS), is a cost-effective, efficient way of managing global clinical studies. With real-time demand and supply response, IVRS integrates patient recruitment and management with CTSC processes, monitoring inventory levels, initiating manufacturing, and managing distribution to warehouses, depots, and CTSC sites globally. The system also allows supply flexibility, essential for adaptive clinical trials, and helps prevent waste.

Distribution managers need to understand the benefits of IVRS and weigh these against the costs. For studies using a simple design and where the availability/cost of the drug is not an issue, then IVRS would not be appropriate. In these cases simple inventory management mechanisms can be employed, even visual (Kan Ban) systems to indicate a reorder point in depots. Even when the products are in short supply, expensive or have short expiry dates, there are a number of alternatives that should be explored.

There are a range of inventory management systems available. IVRS providers are also starting to offer scaled down, inexpensive systems, recognizing there are a large number of studies where full systems are not appropriate.

Material stability

Supplies that are temperature-or time-sensitive have special requirements. The supply chain coordinator will generally utilize specialized shippers that handle priority cargo to ensure that the temperature is maintained and, upon delivery, supplies are moved immediately to a refrigerated unit and documents expedited. The selected trial country depot should be capable of managing in-country distribution and recovery of samples if needed, and have temperature-controlled storage, following GMP standards.

Companies increasingly want to both monitor and manage temperatures for ambient shipments because they have been tested at standard room temperature (0–30° C or 15–25° C). For air freight, in particular, they are concerned about supplies freezing during shipping. An increasing number of companies are using prequalified shippers to maintain an ambient temperature range.

In recent years, there has been a shift from small-to large-molecule drugs, which require cold-chain distribution. These packages must be shipped in an insulated shipper that will maintain

the correct temperature throughout distribution. Companies may need to not only qualify the drug packaging but also the insulated shipping container and the supply chain pipeline.

If resupply is needed for long trials, the contractor should be capable of delivering supplies at the right time to sites.

Comparator sourcing

Global procurement of branded or generic competitor products on the open market requires considerable skill and rigorous quality assurance and analytical processes to ensure that the product is genuine.

A dedicated global project manager with a knowledge of local requirements is best equipped to obtain genuine comparator products and ensure preferred lot availability, expiration dates, and pricing. The manager will source directly from manufacturers and authorized distributors, and also qualify suppliers, the supply chain, and product.

If the product is available in two markets and is more expensive in one, a skilled comparator sourcing expert will first establish product equivalency to get the best price. For example, a product available in both the EU and United States may only differ in color, but the particular dye used in the EU product may not be acceptable in the United States. Liquid medications may also use different preservatives.

Partnering with a contractor

Major contractors are generally well-equipped to manage the efficient, reliable, flexible delivery of products to sites. They have a broad, reliable global infrastructure, including qualified suppliers, adequate storage capacity, and long-standing relationships with key players. They also have the expertise to navigate import/export channels and regulations, manage licenses and timelines, maintain supply stability, and respond quickly to changes in supply demand.

Careful choice of a CTSC contractor is critical to a successful study. Choose a highly reputable supplier with global experience and resources, the flexibility to adapt to trial changes, proven capabilities in your area, an integrated network, and an affordable price. Check that the supplier has adequate capacity and location of depots and is U.S. GMP-compliant if you are seeking FDA approval.

Supply chain managers are increasingly developing strategic partnerships with only a few major full-service contractors for multiple functions, which simplifies supply chain management. Such alliances also enable companies to have access to larger scale innovations, capabilities, and expertise, and thereby realize the cost savings.

Experienced contract distributors are uniquely qualified to help manufacturers succeed in these uncertain times. Developing a sound strategy and clearly defining procedures, roles, and time frames are essential for a successful partnership and ensuring the timely global delivery of clinical supplies.

Notes

Exporting to China, China's Laws, Standards, and Customs Regulations,http://www.export.gov/china/exporting_to_china/importregs.asp|~http://www.export.gov/china/exporting_to_china/importregs.asp/[6].

Central Drugs Standard Control Organization, Directorate General of Health Services, Ministry of Health and Family Welfare, Government of India,http://www.cdsco.nic.in/|~http://www.cdsco.nic.in/ [7].

Israel, Department of Import Policy,http://www.israeltrade.gov.il/NR/exeres/4839496D-02EA-465B-B260-D37F276EB1B9.htm|~http://www.israeltrade.gov.il/NR/exeres/4839496D-02EA-465B-B260-D37F276EB1B9.htm [8].

IATA Cold chain Best practices,http://www.iata.org/ps/publications/9526.htm|~http://www.iata.org/ps/publications/9526.htm[9].