

Global Supply Chain

Best Practices for Clinical Trials

Table of Contents

1	Introduction <ul style="list-style-type: none">▪ The Value Proposition of an Outsourced Global Supply Chain Strategy
3	Global Clinical Trends
5	Best Practices for Global Supply Chain Management <ul style="list-style-type: none">▪ Develop Clinical Logistical Support▪ Create Synergistic Partnerships▪ Harmonize Regulatory Strategies▪ Reduce Waste and Risk▪ Develop a Flexible Structure▪ Establish a Global Team▪ Think Globally, Act Locally
12	Supply Chain Tools and Capabilities <ul style="list-style-type: none">▪ Supply Chain Management▪ Supply Management Process and System Specification▪ Interactive Response Technology▪ Clinical Liaison and Site Feasibility Support▪ Demand Forecasting▪ Resupply Management▪ Global Project Management Reporting
14	Conclusion
15	About Fisher Clinical Services
15	References

Introduction

Now, more than ever, with companies under intense pressure to shed fixed assets, manage costs, and increase efficiencies, they are turning to strategic outsourcing partners to fill global supply chain needs.

Even before the recent economic downturn, the pharmaceutical industry has been steadily and increasingly outsourcing non-core services such as packaging, labeling, analytical testing, and logistics as a means of driving down costs. Now, more than ever, with companies under intense pressure to shed fixed assets, manage costs, and increase efficiencies, they are turning to strategic outsourcing partners to fill global supply chain needs. From large pharmaceutical companies intent on downsizing facilities to biotech and mid-size pharmaceutical companies that do not have the scale required to compile and distribute investigational drugs to sites located in emerging regions of the world, all are recognizing just how labor and regulatory-intensive as well as capital-intensive this part of clinical development is for their organization.

The clinical supply chain is composed of a series of discrete functions that map up to an integrated distribution network responsible for packaging, labeling, and shipping investigational drugs, and managing re-supply as well as returned product from all around the world. Having the infrastructure to accomplish this is no small task and requires a team of skilled experts across a multitude of areas, annual training and certification, and state-of-the-art equipment with high annual maintenance requirements. The alternative is to assemble expertise from either a series of outsourced specialty providers and to integrate those activities or to partner with a clinical supply chain management organization.

The clinical supply chain impacts dozens of functional areas and is critical to a company's success. A supply chain that is not managed properly can negatively impact the lead time for conducting clinical trials and hamper the launch of a new product. While the industry often focuses on subject enrollment and recruitment as the single driver of trial success, it is equally important that the right drug is at the right site at the appropriate time, in compliance with local regulations, in order for those patients to be treated and the trial to proceed.

Organizations recognize the tremendous benefits that a well-managed supply chain can provide to both the top and bottom line and are trending towards a model that outsources the majority of these activities to proven and trusted outsourcing partners whose core capabilities lie in supply chain management and who are

Introduction (continued)

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equipped to address traditional as well as new, supply chain challenges, such as navigating a web of evolving government regulations for drug importation, dealing with highly sensitive products requiring special handling and controlled environments, and managing complicated logistical issues in countries plagued by limited infrastructure and experience.

Short-term cost and productivity measures alone are not enough to meet the fundamental challenges the pharmaceutical industry now faces. With the rising tide of biologics and the expansion of clinical trials to the less developed regions of the world, any company that wants to fend off the risks and exploit the opportunities that are currently emerging will need to submit its supply chain to a radical overhaul. The supply chain of the future must be smart, efficient, and agile.¹

According to a recent report, the development of new R&D network models that help to distinguish the core competencies of a company, its strategic partners, academic alliances, and service providers can help to target productivity issues and achieve cost savings of 40 percent or more.²

As these new models continue to emerge and evolve, outsourcing companies specializing in supply chain management will become more important strategic partners.

Global Clinical Trends

Only 13 percent of clinical trial material shipments arrive on time, and even then, 1 in 10 are incomplete.

While the advantages of going global are many, globalization has, by necessity, driven a significant focus on the supply chain model. Thanks to globalization, the number, size, and complexity of clinical trials are expected to rise dramatically by 2010, forcing sponsors to manage new challenges in the clinical supply chain and complete trials efficiently. Many sponsors do not have the staff, resources, or know how to efficiently manage the regulatory requirements, the import and export challenges, or even the temperature requirements for a new generation of high-cost, highly sensitive investigational products. Today's clinical trials involve investigators in sites from Shanghai to Mumbai; from Kiev to Krakow, often themselves fairly new to the process of clinical development.

According to one survey, only 13 percent of clinical trial material shipments arrived on time and, even then, 1 in 10 were incomplete. This survey suggests that there is a great deal of room for improvement, applying an additional layer of pressure on sponsors.

The increase in the number of clinical trials migrating to sites in Asia, Africa, the Middle East, Eastern Europe, and South America has been accompanied by a host of new issues from a supply chain perspective. This expansionist movement shows no sign of stopping either. ClinicalTrials.gov, the registry of clinical trials taking place in the United States and around the world, recently included more than 72,000 trials taking place in 166 countries.

There are a host of obstacles — internal and external — that can impact the clinical supply chain. Just the sheer number of the different parties involved in the clinical supply chain — from manufacturing to quality control to the clinical teams to supply managers to the regulatory groups — makes the process unwieldy to manage. The complexity of the process is multiplied when the number of countries or regions involved increases, not to mention the numbers of patients involved in studies. Further complicating the model is the complexity of the study design or data collection process.

And at the core of this process is the compound which may be stable or unstable or highly sensitive to temperature changes, air, or humidity.

Global Clinical Trends (continued)

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The biggest challenge of all, however, is the globe itself. Different time zones, local nuances in both regulation and culture, and substandard infrastructures are all logistical obstacles that will continue to challenge outsourcing providers and sponsors alike for the near and long-term.

Best Practices for Global Supply Chain Management

As the number and complexity of global trials grow, the lack of a proper supply chain management strategy sharply raises the likelihood of issues and even delays in clinical trials, resulting in significant costs to sponsors already facing economic pressures.

As the number and complexity of global trials grow, the lack of a proper supply chain management strategy sharply raises the likelihood of issues and even delays in clinical trials, resulting in significant costs to sponsors already facing economic pressures. As such, large and small pharmaceutical companies will increasingly require supply chain management expertise to take a project management approach to deliver specialized skills early in the planning stages. With a specialized approach to supply chain management, companies can improve efficiencies for a number of processes, including pack configuration, multilingual labeling, and inventory control. This will ensure the receipt, packaging, storage, and distribution of clinical trial materials worldwide. This outsourcing approach allows Quality Assurance (QA) teams to support every project, ensures Standard Operating Procedures (SOPs) are strictly implemented, and that current Good Manufacturing Practices (cGMP) are rigorously executed.

Clinical supply providers have exposure to large multinational trials and thousands of protocols every year across numerous therapeutic areas. As a result, providers are able to develop industry best practices for clinical logistical support, allowing for synergistic partnerships, better regulatory strategies and developing an overarching global strategy with local tactics.

Develop Clinical Logistical Support

Best Practice: Develop a comprehensive logistical supply plan. Managing the many moving parts of a supply chain is one of the most time-consuming and intricate of all the factors involved in the clinical process. Logistical support involves engaging strategically placed facilities and depots around the globe to ensure that a supply chain solution is executed that addresses both the regional and country level requirements of a clinical program. An experienced logistics team brings unsurpassed knowledge to the challenges associated with shipping investigational products across the globe.

Additionally, the increased complexity of trials taking place in secondary and tertiary regions requires special handling of biologics, including vaccines and monoclonal antibodies, which require controlled temperature conditions during shipping and storage. From a logistical perspective, the increase in trials of biologics means the

Best Practices for Global Supply Chain Management (continued)

A capable supply chain partner needs to have the resources to manage, track, and transport all types of products, including temperature-sensitive compounds.

stakes couldn't be higher since loss of temperature control requires replacement of costly product. First and foremost, complying with Good Distribution Practice (GDP) during the movement of product is mandatory for ensuring that material integrity is uncompromised. A capable supply chain partner needs to have the resources to manage, track, and transport all types of products, including temperature-sensitive compounds. An outsourcing partner can also monitor materials in transit using different types of technologies, including radio frequency identification (RFID) transmitters that can continuously monitor temperature-sensitive products.

An expert in logistics can also ensure that products do not sit for extended periods in customs where the risks of temperature excursion threaten the viability of a product. For sponsors, it is important that they engage a supply chain outsourcing partner that has a thorough knowledge of the policies and regulations governing import and use of study drugs in trial markets. Such knowledge can help to prevent prolonged customs delays in countries like China, where jurisdictional disputes such as a refusal by regional authorities to recognize drug import licenses issued by national authorities are all too common. Since local country policies and regulations are known to evolve and change without notice, especially in emerging markets, remaining current on the rulebook is a top priority.

Another key strategy is the use of a premium courier company, with a local presence, to assist with managing the often time-consuming customs clearance. Ground handling on arrival is a highly vulnerable point in the clinical supply chain, especially with respect to temperature-sensitive materials. The use of performance metrics in selecting the right courier companies can go a long way to ensuring reliable, on-time delivery of product.

The use of a centralized, regional distribution center to receive trial materials improves distribution and logistics efficiencies while limiting the times when a trial drug must pass through customs. Coordination of customs transit locally is also a prerequisite to successful supply chain management.

The distribution center will receive, book and inventory trial drugs using standard operating procedures (SOPs) and a single information technology (IT) system to ensure transparency and prevent inventory issues over the course of a trial. Inventory

Best Practices for Global Supply Chain Management (continued)

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control with respect to biologics is particularly critical because shelf life is not definitively known in the early testing stages and product could fall out of specification in the course of a trial.

The job of the supply chain manager doesn't end once trial materials arrive at individual clinical sites. The supply chain manager must work closely with each site to ensure that storage locations for temperature-controlled drugs are appropriate, controlled, and secure, and that the staff understands these special requirements. That's when an understanding of local language and culture comes in handy, along with good relationships and the ability to read between the lines. In many countries — China, India, and Japan among them — a high level of cultural courtesy can make it difficult for people to say no. The ability to not just interpret but truly understand what is actually being communicated is essential, saving time, money, and face for all concerned.

Create Synergistic Partnerships

Best Practice: Get started as early as possible. It's important that providers and sponsors work together early on the protocol design, which allows the outsourcing partner to engineer automated solutions and consolidate non-sequential steps to speed progress and reduce risk throughout development.

Similarly, having an outsourcing provider on board earlier when, for example, a global trial is in the planning stages rather than when the pressure to ship product to clinical sites is building, can make a major difference. Clinical Supply Teams comment that their most strategic sponsors bring them aboard in the earliest stages of planning a trial, when the protocol concept and list of target countries are in development, enabling the supplier to begin mapping out deployment strategies months before trial materials are scheduled for packaging and shipping. Sponsors should utilize their supply chain partner as an integrated support system, rather than the provider of discrete functions.

Additionally, a fair amount of savings — time and money — can be achieved to streamline the clinical supply chain if both the project management plan and the supply

Best Practices for Global Supply Chain Management (continued)

The widespread adoption of harmonization guidelines has gone a long way to ease regulatory requirements, but it's still critical to know how to work with sponsors and governments in both ICH and non-ICH countries.

chain plan are done in collaboration. By communicating early on, the partners can address any number of questions before they arise, such as what countries to choose based on not only patient recruitment but the likelihood of timely delivery of drug to sites, gaining an understanding of the impact of import and export regulations could have on trial and project timelines, developing a strategy for re-supply and returns early on in the process, and as a whole, partnering to ensure that the project plan is devised to minimize the administrative burden on the sites themselves to allow them to focus on the clinical concerns of the trials.

Harmonize Regulatory Strategies

Best Practice: Work collaboratively with regulatory authorities. Perhaps the single most important factor enabling globalization is the substantial progress to date in the harmonization of regulatory strategies. To make drug development more seamless means that both sponsor companies and service providers need to work in collaboration with regulatory bodies, around the globe, to develop more common approaches that can eliminate waste, assure patient protection, and streamline the ability to design and deploy a global clinical trial in a much more effective way than has happened in the past.

Since its formation in 1990 by regulatory authorities and research-based industry representatives of Europe, Japan and the United States, the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use — ICH for short — has improved the way drugs and vaccines are developed and registered by eliminating redundancy. Driving the need to rationalize and harmonize regulations were concerns that are even more relevant today than they were then: rising healthcare costs, escalating R&D expenses, and the pressure to make new treatments for cancer, HIV, heart disease, and other serious diseases available to patients in need with a minimum of delay.

Nearly two decades later, pharmaceutical companies can do what was not possible then — demonstrate the quality, safety and efficacy of a new drug or vaccine using a single set of clinical studies, provide these data to regulatory agencies in a common format and importantly, do so electronically.

Best Practices for Global Supply Chain Management (continued)

Fisher Clinical Services estimates, there is upward of 200 percent waste in the supply chain. Accordingly, there is tremendous focus being placed by pharma and biotech customers on managing their internal resources.

The widespread adoption of harmonization guidelines has gone a long way to ease regulatory requirements but it's still critical to know how to work with sponsors and governments in both ICH and non-ICH countries. Today's clinical supply experts must have the requisite knowledge to develop and register new products and streamline the process across an ever-expanding landscape of countries and regions.

Reduce Waste and Risk

Best Practice: Reduce overages and control risks. According to Fisher Clinical Services estimates, there is upward of 200 percent waste in the supply chain. Accordingly, there is tremendous focus being placed by pharma and biotech customers on managing their internal resources. Sponsor companies are focusing on the broader cost of resources that need to be applied internally to assure a risk-free clinical supply chain.

Sponsors typically have a 20-week timeline from final protocol to putting clinical trial supplies in the field. Those supplies can range from the investigative drug to a series of equipment and other ancillary products required by the protocol. These accompanying supplies can range from an ECG machine to home tests for patients, to even food supplements. A holistic approach to the clinical supply process, that takes into account all in bound supplies to an investigative site and develops a plan to optimize the shipping and thereby streamline what is sent to the site, can yield unexpected and sometimes substantial benefits for everyone. Administrative burden is reduced on the sites and the CRAs tracking the materials and economies of scale from consolidating shipments can even reduce the overall logistics budget.

Develop a Flexible Structure

Best Practice: Cut across silos. Because companies' pipelines ebb and flow, gaps develop and it's becoming economically unfeasible for sponsors to carry the costs associated with these products internally. An outside provider, because of its scale of operations, can be more flexible with its resource deployment. Larger outsourcing

Best Practices for Global Supply Chain Management (continued)

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Increasingly, multinational contractors and joint-venture partnerships have established services in tertiary markets to address the industry's hunger for globalization, as well as the integration of discovery and clinical services. As the secondary and tertiary contract marketplace expands, it will enable pharma players to selectively tap into expertise and technological advances within specific markets, thus providing greater R&D flexibility and helping companies to maximize their return on offshore investment from variable overheads through improvements in productivity, competitive pricing, and without locking in significant investment in fixed overheads abroad.³

Third parties often have the ability to span across organizational structures better than the company's internal supply chain team. An outsourcing partner can communicate across silos and connect with all of the functions involved — from logistics to manufacturing to study teams — across geographies and divisions to manage the internal and external communications and planning. However, to achieve optimal results, there must be trust and open communications between the sponsor and outsourcing partner. The service provider can't over promise and under deliver — the stakes are too high. Likewise, the sponsor needs to readjust its management model from one based purely on transactions and projects to a strategic model based on long-term and mutually beneficially relationships. The most successful models are ones where the sponsor has looked to partner with a provider that can help them access all challenging geographies, rather than a select region only. Sponsors who have developed the sort of trust with their outsourcing partners that allow them to share plans in advance can gain the benefit of these providers investing for them in regions or technology.

Establish a Global Team

Best Practice: Team management. The globalization of the pharmaceutical industry is taking place at every level, including that of the workforce. Multinational programs have grown to include non-traditional markets, and establishing a strong

Best Practices for Global Supply Chain Management (continued)

What sponsors need to consider, and this is where a global outsourcing partner can lend assistance, are the local challenges involved with the clinical supply chain and a proactive plan for addressing and managing those risks.

global team takes time, just like any relationship. The hurdles are particularly high, however, when the team is spread across continents and time zones.

A clinical trial supply expert brings more than simply the resources to establish a global team — he or she also bring a deep understanding of the various cultures and have had experience in creating a shared sense of mission and goals within the clinical supply chain and with their clinical partners. While every multinational clinical trial requires an entire cast of specialists to achieve success, all too often these time-sensitive and complex programs dissolve into various camps and fail to recognize that all contributors are united by a common mission. Identifying the right partner means more than years of experience or training, it requires ensuring that these teams work well with others, understand a multi-cultural environment, operate well under pressure, and adjust for unexpected challenges. This uniting concept translates across borders, regions, countries, languages, and cultures.

Think Globally, Act Locally

Best Practice: Implement local tactics. All clinical trials are local. A global clinical trial plan is necessary, but too often, the approach to clinical trials planning, materials planning and patient recruitment is done under the guise that global means everybody is the same. What sponsors need to consider, and this is where a global outsourcing partner can lend assistance, are the local challenges involved with the clinical supply chain and a proactive plan for addressing and managing those risks.

In the near-term, offshore investment has focused on many of the secondary emerging economies, such as the BRIC (Brazil, Russia, India, and China) nations, to contract preclinical and clinical research. In the longer term, the tertiary, third-tier economies will emerge to capitalize on specific skill sets and take advantage of the cost differentials and/or infrastructure benefits to attract additional offshore investment. Tertiary markets, such as Australia, Argentina, Chile, Turkey, Pakistan, Peru, South Africa, Ukraine, and Vietnam are increasingly evolving to fill market niches and service smaller specialist companies, thus tapping into a rapidly growing marketplace. A supply chain partner with local expertise will become an invaluable asset.

Supply Chain Tools and Capabilities

An outsourcing partner should have key capabilities in such areas as: supply chain management, supply management process and system specification, interactive response technology, clinical liaison and site feasibility support, demand forecasting, resupply management, global project management reporting.

An outsourcing provider's technical supply chain capabilities allow their experienced staff to systematically handle and improve all critical processes for their sponsor partners. They can help cut costs by consolidating multiple vendors into fewer strategic alliances, drive profitability by removing non-core services from the portfolio to fund other strategic investment and grow revenue by transforming fixed costs into variable. An outsourcing partner should have key capabilities in such areas as: supply chain management, supply management process and system specification, interactive response technology, clinical liaison and site feasibility support, demand forecasting, resupply management and global project management reporting.

Supply Chain Management: By focusing on the demands of a client's clinical protocol, a partner can deliver levels of performance and efficiency, and better manage risk.

Supply Management Process and System Specification: Make higher-level decisions earlier to minimize drug and supply waste without compromising patient safety.

Interactive Response Technology: Observe and control critical trial details at every site in the study through any real or virtual desktop by using interactive response technology. Retain total control of any investigational product or ancillary supplies used by an investigator site from the day it is planned, designed, packaged, managed, quality controlled, re-supplied, replaced, or expired.

Clinical Liaison and Site Feasibility Support: Know how to best receive and handle investigational products and have the confidence that enough of the right temperature-controlled capacity exists to meet your needs comes from working with worldwide experts in GMP. By understanding the dynamics of site demand and supply, sponsors can best support clinical research functions at the investigational site level with accurate forecasts and appropriate supply of investigative product or ancillary supply without waste.

Demand Forecasting: Analysis tools and techniques help sponsors forecast likely potential scenarios for cost-effectively sourcing bulk product and comparator, high

Supply Chain Tools and Capabilities (continued)

cost or other high touch products, determining production capacity, or projecting finished clinical materials or ancillary supplies.

Resupply Management: Knowing the endpoints, the goals around patient compliance, and the cost-containment requirements, a process can be designed and engineered to cost-effectively optimize a sponsor's supply chain. Serving local markets in their own language, experts listen first, hear needs and are motivated to serve as an extended team to meet the demands of a clinical protocol.

Global Project Management Reporting: A robust information infrastructure helps sponsors closely manage all aspects of their clinical supply chain — from the procurement of comparators to the impact of recruitment levels at sites to the management of returns and destruction. Near real-time reports also help to preemptively manage risk in the clinical protocol with the visibility needed to make the next right decision to ensure quality and compliance within exacting regulatory and variable international standards.

Conclusion

Sponsors should look to partner with an organization with demonstrated expertise, ability to work across geographies and cultures, a keen understanding of local and international requirements, and that offer models for support at multiple levels.

In today's challenging financial and global environment, with higher cost investigational drugs, one of the most critical considerations for clinical development is how to minimize risks in the clinical supply chain. A set of tasks that were historically seen as in-house activities by pharmaceutical organizations are increasingly being outsourced to organizations with more capacity, a broader footprint and available resources to help them with the growing complexity of clinical programs and the expanding network of clinical sites.

It is critical for clinical and clinical supply teams to initiate planning and collaboration early in order to proactively plan for any potential challenges that would delay in shipping drug to sites when it is needed. Sponsors should look to partner with an organization with demonstrated expertise, ability to work across geographies and cultures, a keen understanding of local and international requirements, and that offer models for support at multiple levels.

About Fisher Clinical Services

Fisher Clinical Services is a leading provider of global clinical supply solutions. We offer our customers access to the capacity, state-of-the art equipment and processes of the industry's largest packaging and distribution supplier for clinical trials with locations strategically placed across the world to support clinical research. Our services include labeling, comparator sourcing, clinical manufacturing, overencapsulation, packaging, kitting, logistics, ancillary supply management and return drug destruction and accountability.

Fisher Clinical Services is a part of the BioPharma Services Division of Thermo Fisher Scientific, the world leader in serving science, enabling our customers to make the world healthier, cleaner and safer. With annual revenues of \$10 billion, the company has more than 30,000 employees and serves over 350,000 pharmaceutical and biotech companies, hospitals and clinical diagnostic labs, universities, research institutions and government agencies, as well as environmental and industrial process control settings.

To hear an accompanying Podcast featuring Patrick Durbin, Vice President of Fisher Clinical Services, as he speaks about Global Clinical Trials Outsourcing: New Tips and Trends, visit <http://www.fisherclinicalservices.com/mediaroom.php?id=29>

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