PEER REVIEWED

What Clinical Teams Should Know about Changing Trial Logistics and How they will Affect Development – PART 1

When it comes to clinical supplies, the journey is every bit as important as the destination. And these days, the journey of clinical supplies to investigator sites is becoming costlier and more complex, much like the global trials for which the materials are bound.

The price of failure is high. A supply shortfall, or the inability to deliver needed supplies to clinical sites, can delay the start of a trial or cause an ongoing one to grind to a halt. Supply shortages can imperil an entire development programme and prevent study patients from receiving the drugs a sponsor has committed to provide.

It's no wonder that supply chain logistics are estimated to account for as much as 25 per cent of total annual pharmaceutical R&D costs.[1] These cost pressures are projected to grow as a result of an evolution that is altering the clinical trial landscape and generating complex supply chain challenges. Some examples of that evolution in progress include:

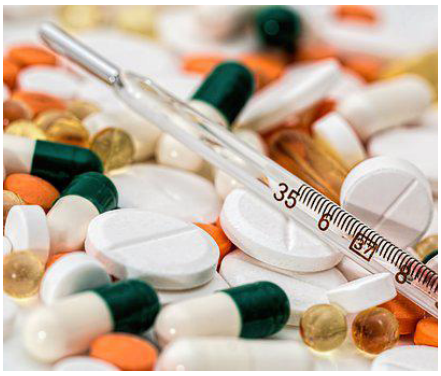
- The explosion of cold-chain products in development and move toward shipping even ambient products under temperature controls
- The continuing globalisation of trials and impact of supplying trials in remote emerging market locations
- Evolving importation regulations and the potential fallout for imprecise documentation
- The soaring demand for comparator alongside concerns about safeguarding the integrity of the supply chain
- The growing interest in and potential of direct-to-patient studies
- Emergence of what one supply chain manager has dubbed an "Amazon-like culture"
- The need for flexibility and contingency planning in a crisis-du-jour world

Much in the way that a GPS constantly adjusts to accommodate shifting traffic patterns and other obstacles, clinical supply chain logistics are adapting to accommodate these developments.

In addition to discussing how supply logistics are changing, this paper contains examples of how Fisher Clinical Services is deploying flexible solutions to ensure secure, efficient and cost-effective passage of clinical supplies.

Challenges and Logistical Costs Escalate

'The more things change, the more they stay the same' could easily apply to the biopharmaceutical industry today.

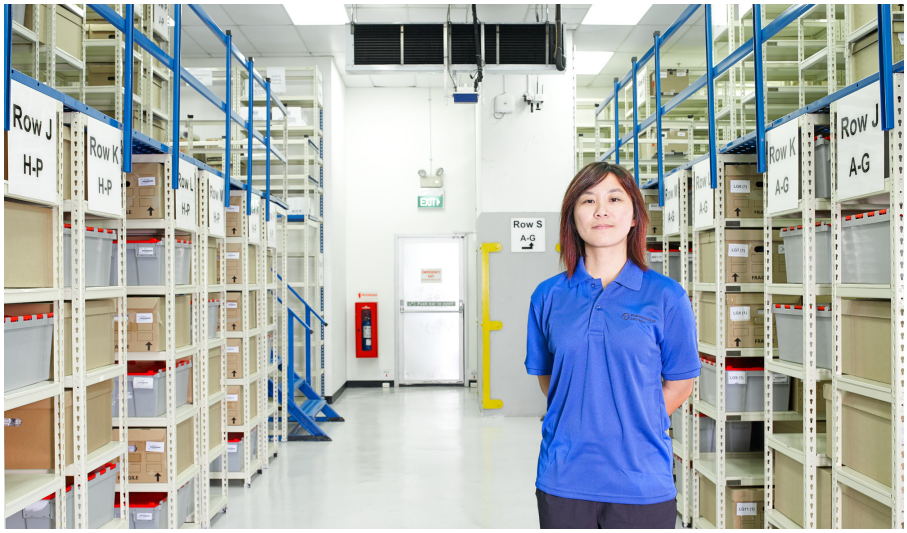


Despite the ever-evolving nature of the industry, drug development remains a lengthy, complex and costly process. A growing list of challenges is constantly exerting new pressures on the industry: An aging population, the growing cost of healthcare, pressure from every quarter about the cost and safety of drugs, barriers to entry in emerging markets, the wider adoption of generic drugs and keen competition among companies, not to mention increasingly difficult therapeutic targets.[1]

Now, add to this list the burgeoning cost of logistics for clinical trials. Logistics spending has been on the rise and is projected to increase steadily. Spending on global biopharmaceutical logistics was $72.5 billion in 2014, increased to $78.8 billion in 2016 and is expected to reach $85.8 billion in 2018. By 2020, such spending is projected to climb to $93.8 billion, driven in large part by cold-chain logistics.[2]

Even with escalating logistical costs, the role of supply chain in the pharmaceutical industry remains underappreciated. Only 39 per cent of pharmaceutical respondents viewed the supply chain as an equally important part of business success as R&D, marketing and sales, according to a 2014 survey.[1]

This leaves the industry warily eyeing escalating logistics costs and



considering how to reduce them safely. As a US-based supply chain manager put it, “Everyone wants to know what that secret sauce is in terms of getting drugs from Point A to Point B with the least amount of risk at the lowest cost.”

Eye on Supply Chain: Logistics 2.0

Call them change-makers, transformers, disrupters. Whatever the name, the six developments discussed here were named by supply chain managers as driving the ongoing evolution in the clinical trial arena. Each of these developments is generating or will generate complex supply chain challenges that demand innovative, flexible and sophisticated solutions.

Falling Temperatures

The explosive growth of biologics is making cold the new normal and cold-chain management one of the biopharmaceutical industry’s major concerns.

Biologics have been nothing short of a resounding success story for the biopharmaceutical industry, heralded for making giant leaps forward possible in the long-term treatment of cancers, diabetes, rheumatoid arthritis, kidney failure and multiple sclerosis, as well as orphan and other diseases. So it should be no surprise that the primary driver of supply chain costs is the explosion of therapies that require cold storage.

In fact, there appears to be no end in sight.[2,3]

By 2020, greater than half of bestselling drugs will be cold-chain products, most of which are injectable.[4] The growth of the global biosimilars market – which could reach $35 billion by 2020 – is a key contributing factor.[3]

Maintaining a secure cold-chain through storage, handling and transportation of temperature-sensitive drugs – some worth $1500 per vial – ensures product quality and integrity and compliance with various laws, regulations, guidelines and codes. Cold-chain handling is drawing increased regulatory interest, with both governments and industry updating cold-chain rules in the past decade and expanding the scope of temperature monitoring and control.[5]

Shipping products, whether they must be maintained in the cold

chain or under controlled ambient conditions, is expensive. To pack and transport materials in the cold-chain, and to demonstrate by process qualification or by measurement that shipments remain cold, merely adds an additional level of complexity. In short, preventing temperature excursions comes at a cost – and costs are climbing.

In 2018 alone, logistics for cold-chain products alone are expected to cost drug-makers $14.4 billion, a price tag projected to reach $16.7 billion in 2020.[2] This includes specialised tertiary packaging and instrumentation such as insulated boxes, blankets, phase-change materials, active temperature-control shipping containers and various temperature sensors and recorders. It also includes air, parcel and truck service.[4]

Even as costs for cold-chain logistics skyrocket, an increasing number of products are likely to be transported under colder conditions. Regulatory authorities have indicated their preference for shipping all drugs under controlled temperature conditions. A reason for this is differences in interpretation about what constitutes ambient conditions, according to one supply chain manager. A number of Asian countries, including China, considers 0–30°C. to be ambient. Meanwhile, ambient is defined as 15–25°C. under Good Manufacturing Practice (GMP) standards.

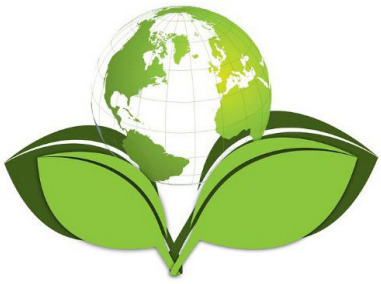
Sponsors are beginning to ship even ambient drugs, such as capsules and blister packs, under controlled temperatures accompanied by temperature monitors. There is also a move toward shipping temperature-controlled products as frozen shipments, making cold – and colder – the new normal.

Fostering Innovation

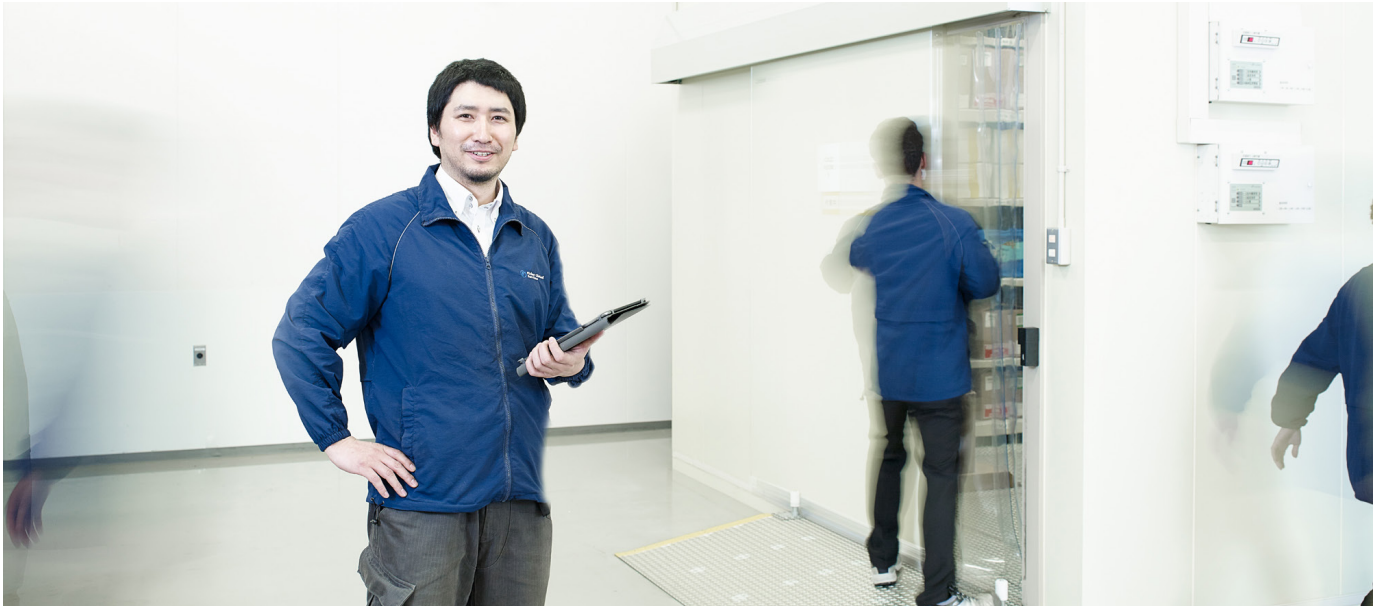
It's not a surprise that these developments are increasing the demand for cold-chain services and new packaging and temperature-monitoring technology. At Fisher Clinical Services, half of all 2016 shipments were temperature-controlled compared to a quarter of shipments five years ago.

The company is addressing these needs with continued investment in cold-chain storage, distribution capability and expertise across its global network, enabling it to handle growing quantities of cold-chain biologics across the globe:

- In Asia Pacific, Fisher Clinical Services more than doubled cold-chain capacity for the region with the opening of a new 70,000-square-foot cGMP facility in Singapore and the expansion of the Tokyo, Japan facility.
- In Europe, the company doubled cold-chain capacity in Basel, Switzerland. Fisher Clinical Services also became the first supply chain partner in the industry to make fully automated assembly and labelling of pre-filled syringes from 2°C. to 25°C. Introduced in 2017, this service is exclusively available at the Basel facility, where a dedicated cold facility maintains cold-room conditions from truck to dock, through assembly, storage and distribution.
- In Africa, Fisher Clinical Services extended the cold-chain capabilities of its facility in Pretoria, South Africa.



Fisher Clinical Services also continues to explore and adopt new packaging and technology, including the use of robust, reusable shippers that reduce the burden on investigator sites and the



environment. In 2016, for instance, Fisher Clinical Services partnered with a sponsor on a pilot programme using a high-performance, phase change material (PCM) reusable shipper.

The results were encouraging. In addition to resulting in a lower temperature excursion rate and greater contingency for delays than traditional, single-use shippers, the reusable shippers were lighter and cheaper to ship. While more expensive, the reusable shippers compensated for a higher price tag by significantly reducing waste and environmental impact.

The sponsor estimated that the use of reusable shippers would divert 300,000 pounds of waste from landfill in year one, with a targeted reduction of 1.2 million pounds diverted from landfill in year two. Investigator sites similarly gave their thumbs-up, citing the reduced burden and expense of shipper storage and disposal.

Increasingly Global Studies:
Continued globalisation is increasing logistical challenges as more clinical trials migrate to emerging markets.

In pursuit of faster, less expensive recruitment for clinical trials, sponsors continue to target emerging markets. It is worth noting that most studies continue to take place in North America and Western Europe. However, most of the growth in clinical research is taking place in Asia, South and Central America, the Middle East, Africa and Eastern Europe.[6]

> While an enlarged clinical trial universe undoubtedly benefits patient recruitment and diversity, it also multiplies the logistical obstacles for supplying studies.

In addition to inexperience in conducting trials and differing quality standards, there are widespread differences from country to country in Customs knowledge, experience and laws.

Many developing countries are also evolving regulatory requirements about the conduct of clinical trials and protection of research subjects. Some are implementing stringent new regulations for importation and clinical research.

Failure to adhere to these rules, particularly with respect to documentation, could derail timelines and budgets. In countries such as China, Russia and Ukraine, for example, failure to provide an acceptable rationale for product valuation can result in immediate and future headaches. In addition to higher costs due to revaluation and a fine, the sponsor can look forward to having all of its future shipments "examined with a fine-tooth comb," as a United Kingdom-based supply chain manager explained.

There is also the need to manage logistics complicated by countries' challenging climates and limited infrastructure. As previously discussed, studies of temperature-sensitive biologics present additional logistical challenges across the supply chain. Temperature excursions can exact significant drug and financial loss and missed patient dosing. Missed dosing violates the commitment to serve clinical trial patients and can put their safety and wellbeing at risk.

Finally, there are regional idiosyncrasies – differences of language, both spoken and unspoken, working patterns, culture and religion – that add another layer of logistical complexity.

Fostering Innovation
Fisher Clinical Services has the industry's largest network of fully-owned cGMP facilities strategically located around the world to support the conduct of clinical trials. Some 16 purpose-built, GMP/Good Distribution Practices (GDP)-compliant facilities located across five continents provide the global presence, information systems and quality standards to ensure the flexibility, access and assurance needed for clinical trials.

The network of Fisher Clinical Services' facilities continues to grow. In addition to the expansions and new facilities noted earlier, in the last five years Fisher Clinical Services opened its first clinical services facility in Seoul, South Korea, and doubled its presence in China to include a facility in Suzhou, located in a Free Trade Zone near Shanghai.

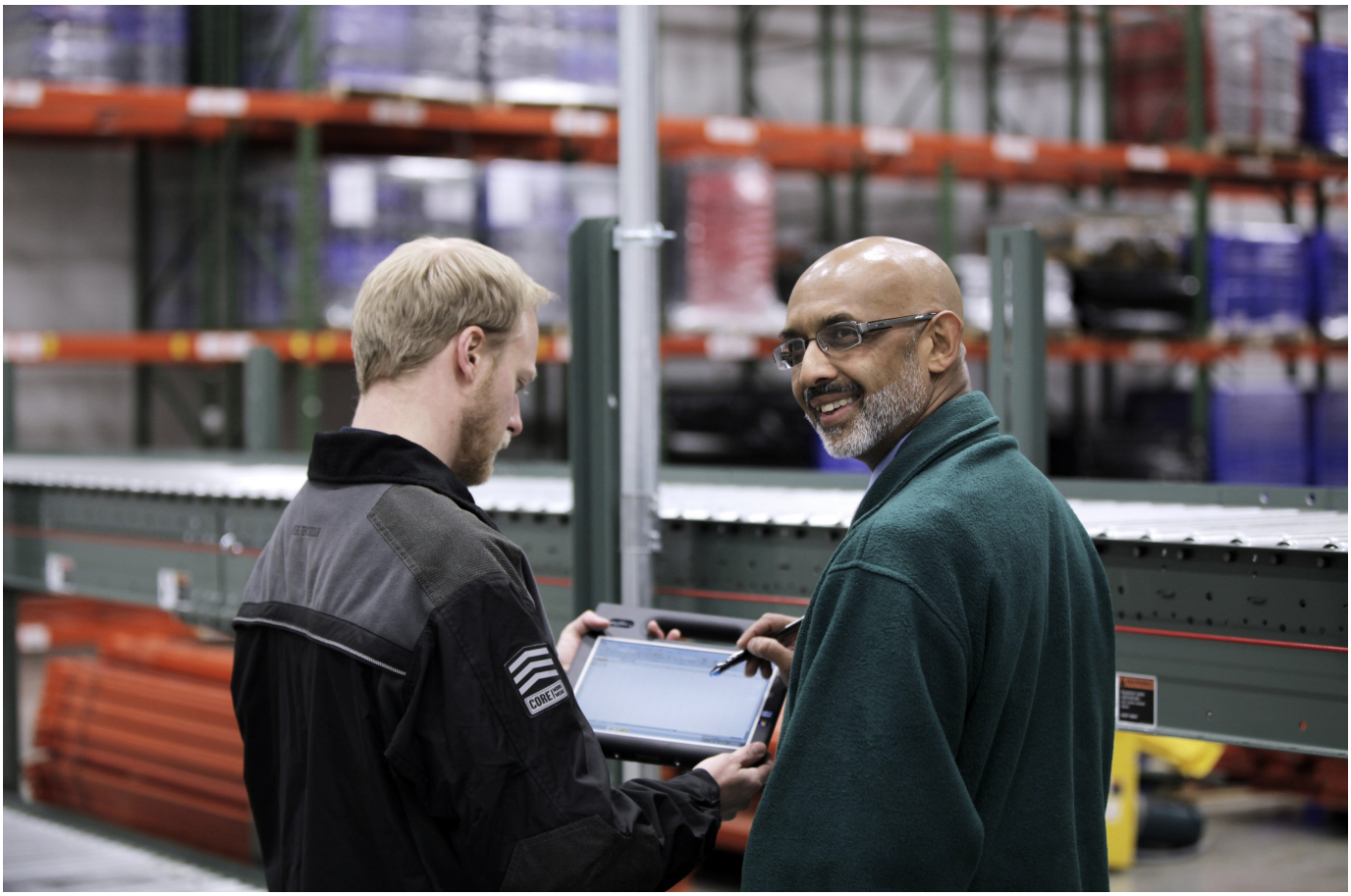
Each facility is staffed with a team of highly-trained professionals who bring a depth of expertise in managing clinical trials, from protocol design to site receipt of clinical materials. Add to this global expertise an understanding of local requirements and regulations, proficiency in the local language and English, and established working relationships with key parties across the supply chain.

Altogether, this allows Fisher Clinical Services to support the regulatory-compliant movement, management and delivery of supplies to more than 150 countries across all therapeutic indications. An example follows.

Case Study 1
How an Innovative Transportation Solution Yielded Efficiencies and Cost Savings

A leading multinational pharmaceutical company with an extensive clinical trial pipeline approached Fisher Clinical Services to develop a comprehensive, fully managed transportation strategy.

The sponsor chose Fisher Clinical Services because of its Total Transportation Management Service, a solution that includes complete oversight of the supply chain processes required to move



investigational medicinal product (IMP) shipments internationally and within countries of choice.

A cross-functional Fisher Clinical Services team – including specialists from Information Technology (IT), Quality, Project Management, Engineering, Operations and Finance – convened. Their objective: Defining supply chain strategies to achieve a maximum percentage of on-time shipments and to realise cost efficiencies. The team analysed trial protocols, consulted a logistics database, evaluated data on couriers and applied data-driven objectivity to route and courier choice.

As a result of these efforts, the sponsor's original transportation strategy was changed to reflect a new approach to courier selection. This data-driven courier selection approach optimised cost and performance efficiencies for the sponsor, achieving significant cost savings.

Previously, the sponsor was sending 32 per cent of its shipments via premium courier. Thanks to the data-driven objectivity applied by Fisher Clinical Services, the proportion of shipments being transported by premium couriers plummeted to 7 per cent, resulting in annual cost savings of $10.2 million. Meanwhile, on-time shipments increased to 97 per cent from 93 per cent.

Short Supply

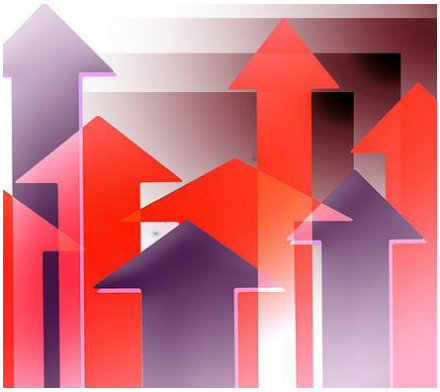
Soaring demand for reference drugs is generating innovative sourcing strategies that must also safeguard the integrity of the supply chain.

The escalating volume and complexity of global trials have driven the demand for reference or so-called comparator drugs to record levels. This is creating pressure to source sufficient quantities of comparator within tightening timelines and budget constraints.

In early 2017, for example, more than 236,000 studies were taking place in 195 countries, a number that has been climbing steadily, according to clinicaltrials.gov, the US registry of clinical trials.[6]

As a result, the challenges of global sourcing for clinical trials have never been greater, particularly in emerging markets. Aside from the sheer number of countries involved in the typical clinical trial, a series of regulatory, supply and logistical obstacles magnify the challenge of sourcing comparators in emerging markets.

Many emerging markets are creating or evolving their regulatory infrastructures. In addition, some suppliers in emerging markets do not adhere to European or North American quality standards and requirements.



Maintaining the integrity of the supply chain is another issue of concern. Drug counterfeiting is escalating worldwide, affecting both developed and developing countries. China and India, two top-ranked countries for clinical trials, have also been identified as the sources of an increasing number of counterfeit drugs. The World Health Organization (WHO) estimates that up to 30 per cent of the drugs sold in parts of Asia, Africa and Latin America are counterfeit.[7]

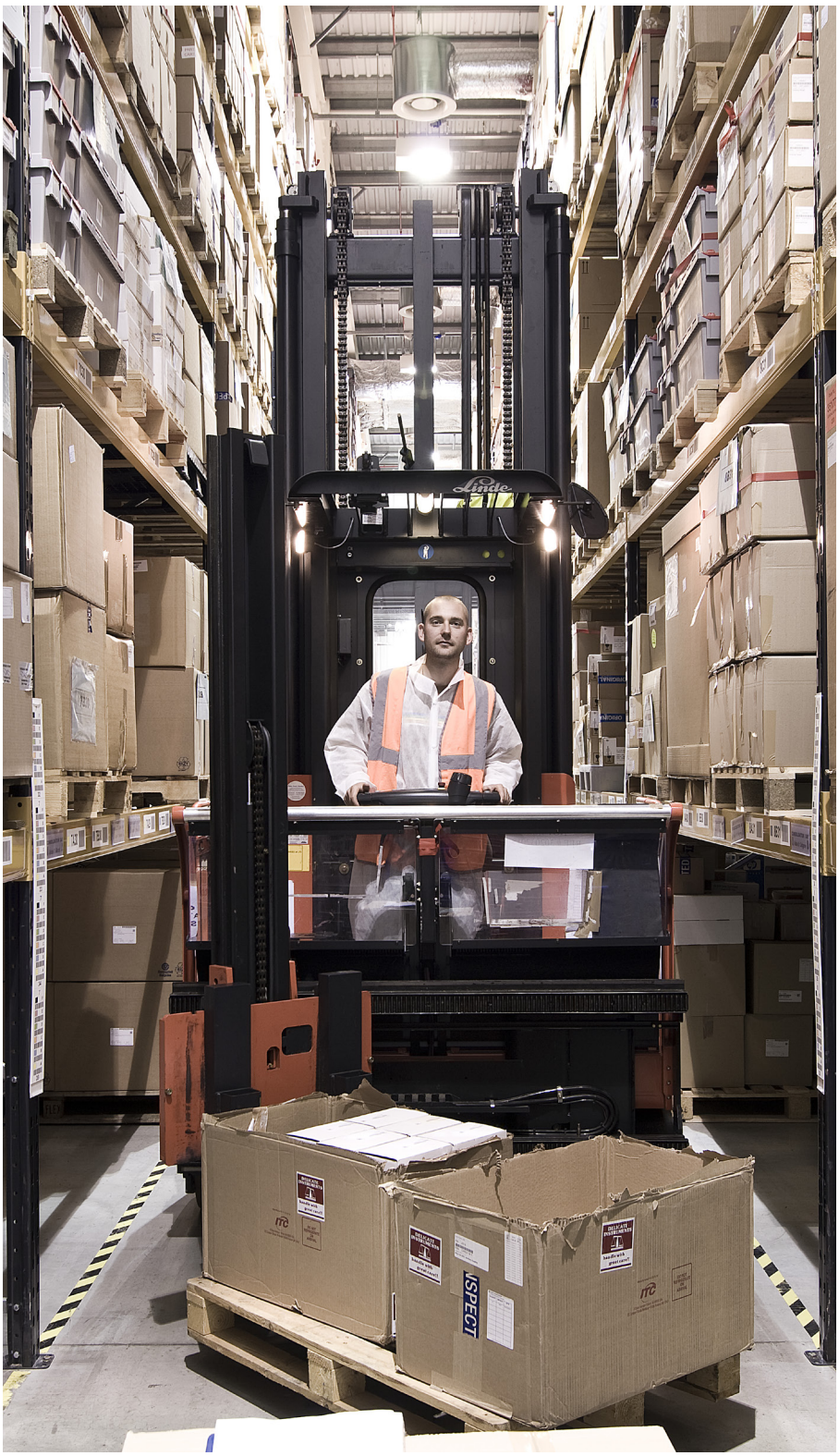
Fostering Innovation

Fisher Clinical Services has a dedicated team of individuals whose sole job is sourcing comparator globally. This team takes the strategic approach of managing supply chain from day one through the conclusion of the trial by maximising options and minimising risk. They begin by assessing the specific risks and challenges in individual markets, and then identify ways to mitigate issues.

Direct sourcing of comparator from the manufacturer is almost always the best option because it establishes the shortest, most transparent supply chain, minimising cost and the risk of counterfeit product. When sourcing from a manufacturer isn't feasible or desirable, however, the team turns to wholesalers and distributors that have been vetted in a rigorous qualification process.

The qualification process includes risk assessments of both the supplier and the country of sourcing. Supplier criteria include reputation and referrals, licenses, capacity, pricing and benefits, economic status and financial stability.

The country of sourcing is key because some markets are safer than others. Country criteria include whether the regulatory authority requires adherence to GMP, GDP and Certificate of Pharmaceutical Product (CPP) standards, legal provisions on marketing authorisation, regulatory inspection of manufacturers and distributors, import control, and licensing and sanctions for violations of codes of conduct. Another element is the frequency with which counterfeit drugs have been documented in the country.



Ultimately, there is no one-size-fits-all sourcing solution. Every sourcing project requires a tailor-made strategy to deliver the best outcome.

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Jennifer Worsfold

Senior Director Supply Chain Solutions – Fisher Clinical Services. Jennifer Worsfold joined Fisher Clinical Services in 1996. A key member of the Global Project Management Leadership Team, Jen is passionate about providing the highest standard of customer service to all Sponsors, always delivering on client expectations. Over the years, Jen has never lost sight of her first priority-“to serve the patient.”

From 1996 to 2006, Jen was based in Fisher Clinical Services Horsham and was instrumental in instilling a focus on the customer. She finalized her tenure there as Director of Logistics and moved to the Fisher Clinical Services Allschwil office in 2006. There she led the Project Management of the Manufacturing, Packaging and Distribution services. In parallel, she set up a new facility in Weil am Rhein as a Warehouse and Distribution Centre for strategic customers within the European Union. Jen’s success is evident in the increasing capacity of the Allschwil facility and in the development of the Weil am Rhein facility. Jen has recently taken on a role as Senior Director for Distribution Services; encompassing all aspects of Customer Service and Project Management whilst also supervising day-to-day operations. A consummate professional, she continues to raise the bar for Quality, Service and Pro-active Project Management at Fisher Clinical Services.

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