Why a Closed-Loop Supply Chain System?

Improving compliance and efficiency
in the pharmaceutical supply chain
with reduced cost and risk

World Courier

In the area of clinical trials, WORLD COURIER delivers unprecedented expertise in the handling, transport, storage and distribution of temperature-sensitive pharmaceutical products and biological specimens for one-stop global clinical supply support.

WORLD COURIER's fully-integrated GxP-compliant pharmaceutical supply chain system features a company-owned network of over 150 transport offices in more than 50 countries with GMP-compliant investigational drug storage depots in 13 strategic and emerging markets, strong knowledge of the local regulatory environment, and well-trained staff who operate according to global SOPs.

Why a Closed-Loop Supply Chain System?

Improving compliance and efficiency in the pharmaceutical supply chain with reduced cost and risk

The International Conference on Harmonization's (ICH) Topic E6 entitled "Good Clinical Practice: Consolidated Guidance" is a commonly referenced industry document that has gained regulatory acceptance in the EU, Japan and the United States. Section 5.14.3 states that "the sponsor should ensure that written procedures include instructions that the investigator/institution should follow for the handling and storage of investigational product(s) for the trial and documentation thereof. The procedure should address adequate and safe receipt, handling, storage, dispensing, retrieval of unused product from subjects, and return of unused investigational product(s)".

Although this regulation is aimed at enhancing GCP at the investigator level, the reality is that most of these functions are executed by, or in conjunction with, third parties − transport, storage and delivery personnel who are, in most cases, untrained in pharmaceutical standards. When taking into consideration that as many as 40% of all clinical trials are now conducted in emerging nations in Asia, Latin America and Africa, most IMP travels thousands of miles over extended periods of time under the guardianship of non-pharmaceutical personnel before arriving at individual research sites. How does the sponsor ensure that product transfer conforms to the same established written procedures demanded at the investigator level throughout the full length of the supply chain, or more specifically while in the hands of non-pharmaceutical, non-investigator personnel?

While these third parties are perforce governed by general GMP directives and specific GSP/GDP guidelines such as from WHO (WHO technical report series no. 957/2010 and no. 961/2011), IMB (Guide to Control and Monitoring of Storage and Transportation Temperature Conditions for Medicinal Products and Active Substances/2011), Health Canada (Guidelines for Temperature Control of Drug Products during Storage and Transportation/2011) as well as from PDA (Technical Report 052/2011), the cornerstone of clinical research rests on the assumption that the IMP arriving at the investigator site meets all legitimate product specifications. Is that, however, a fair assumption? How can this assumption be tested, corroborated, and more importantly, be transformed from conjecture into fact?

Adding to the urgency is today's increased focus on ICH Q9 which calls for more formalized Quality Risk Management (QRM) assessments and decision-making to ensure that long-term product quality remains consistent with key product attributes in evidence during the clinical study. Clearly the need to proactively protect the integrity of clinical products that will ultimately function as quality benchmarks has never been more critical, particularly in the face of the growing complexity and scope of risks precipitated by distant study locales.

Achieving More Stringent External Compliance

Choosing a GxP-compliant logistics supplier that operates a high-quality closed-loop clinical supply chain system ensures that all critical functions outlined in the ICH guidelines − transport and reception of clinical product in-country, its handling and storage, the preparation of patient kits for individual sites, their subsequent distribution, and the documentation and management of returned drugs − are performed by the same service provider from origin right through to destination in keeping with verifiable, global SOPs.

This type of all-inclusive service offering can significantly reduce the cost, risks and inconvenience of dealing with multiple suppliers and effectively eliminate many of the miscommunications, technical errors and conflicting SOPs that are inherent in the hand-off of product between numerous third parties. By offering a full series of complementary services, the closed-loop supply chain provider is better able to deliver customized options that address the sponsor's unique situation without needing to "sell" a specific type of service or make the difficult choice between a sale and the best interests of the customer. The following example illustrates.

One Supplier vs Multiple Suppliers

An international pharmaceutical company is planning a Phase III cancer study in China. The duration of the study is 12 months. Eight in-country sites will participate. The investigational drugs must be maintained within a temperature range of +2°C to +8°C. Each site will receive one shipment per month. The sponsor is considering three different suppliers to provide services. The first (Company A) is an international transportation company. The second (Company B) is a pharmaceutical warehousing company in China capable of storing investigational drugs in-country and arranging for local distribution. The third (Company C) is a closed-loop logistics company able to offer a suite of fully-integrated supply chain services.

True to its organizational capabilities, Company A quotes on a "direct-to-site" solution, proposing that one consignment be shipped to each investigator site each month − 96 shipments in all (8 sites x 12 months). Operationally, each shipment must be consigned directly to the ultimate recipient (the lab or hospital administering that part of the trial), necessitating an individual import permit and separate customs clearance for each shipment − a costly and laborious procedure for the clinical team that can result in indeterminate delays if paperwork is imprecise or incomplete. Should delays prove significant, temperature-controlled mediums can conceivably fail, compromising product quality. In other instances, delays may result in shipments arriving too late to be of use, resulting in missed dosing schedules. With no benefits to be derived from consolidation, this is arguably the most expensive and least effective transport solution. It is based on an old, just-in-time distribution model that pre-dates the advent of local temperature-controlled storage facilities and requires service roll-out that runs like clockwork to avoid unnecessary delays or storage at the investigational site.

In keeping with its business model, Company B proposes an in-country warehousing option that will significantly reduce the number of shipments in transit and with it, the risk for clearance delays. It is proposed that a three-month supply of investigational drug for each site be forwarded to the Chinese warehouse on a quarterly basis, or the equivalent of 24 direct-to-site shipments (8 sites x 3 months). In all, then, just four larger batch shipments will be dispatched during the course of the year-long study. Since the investigational drugs will be centrally stockpiled for in-country distribution, the sponsor will enjoy more flexibility in managing the shipping timeline. Shipments can be sent with enough lead-time to manage any potential customs delays, resulting in less opportunity for missed dosings at the local level. At the same time, the clinical team will significantly reduce the amount of time spent preparing paperwork and import permit applications, and monitoring individual shipments. Transportation costs would also drop significantly, given the greatly reduced number of shipments (four versus 96).

Because Company B cannot execute the physical in-country distribution, however, a new local supplier must now enter the mix. Will a single supplier handle all eight shipments/sites,

or will eight suppliers each handle one? Does/do the local supplier(s) conform with internationally accepted SOPs governing the transport of pharmaceutical products used in clinical trials? Are the local transport providers' SOPs in sync with those of the warehousing company? Who will design, prepare and provide the temperature-controlled packaging − warehouser or transporter? Who is responsible for packing and labeling the shipments? Who will the sponsor or CRO contact if an investigator site does not receive a shipment as planned or if temperatures fall out of specification? Who will assume ultimate responsibility if miscommunications occur, if temperature control fails, or it the product is unusable? A request for the return/destruction of unused medications and supplies creates an equally clumsy, cumbersome and time-consuming process that remains largely devoid of a clear chain of custody. While the simple warehousing solution clearly reconciles many of the inherent transport difficulties that can occur with direct-to-site routings, it also raises many new questions and with them, the potential for conflicting SOPs, human or technical error, and miscommunication.

The final provider, Company C, offers a fully-integrated closed-loop supply chain system that is able to deliver all required services from origin to destination: international transport (including packaging and clearance), local storage in certified facilities, in-country distribution according to a pre-determined schedule, the expediting of emergency shipments and return/destruction capabilities if required − all performed by the same service provider and linked by a single online data system.

By selecting Company C's local warehousing solution, the sponsor enjoys the same economies of scale as outlined above, achieved by shipping four large batch shipments instead of multiple (96) direct-to-site shipments. Transport costs are significantly reduced, but more importantly, so is the manpower expended by the clinical team not only in the preparation of import/export paperwork, but in qualifying third-party vendors, coordinating the hand-off between suppliers, monitoring shipments, and resolving queries and problems that inevitably arise when multiple providers are involved. At the same time, the sponsor also benefits from superior quality assurance and product control including in-country inventory management and a vastly improved chain of custody that can be managed through a single contact or access point. Remedial actions can be anticipated and expedited (i.e. rectifying an inventory shortage by dispatching an emergency replacement shipment) with the ultimate objective of streamlining the clinical trial process, reducing risks and ensuring that in-spec products and materials are where they should be when needed.

In meeting these objectives, the services offered by each potential provider can be summarized as follows:

COMPANY A

Direct-to-Site Solution: 96 *ad hoc* shipments direct to investigator sites

Advantages

- isolation of shipping problems (problems with one shipment do not affect the others)
- relatively simple chain of custody (pharmaceutical company/transport company/investigator site)

Disadvantages

- service frequency and associated escalation of risks
- increased complexity of import process
- excess time spent preparing paperwork, monitoring shipments
- increased possibility of errors
- increased possibility of avoidable customs inspections/delays
- increased possibility of temperature failure
- increased possibility of compromised product quality
- increased possibility of missed dosing schedules
- costliness (no economies of scale to be derived)

COMPANY B

In-Country Warehousing Solution: 4 large batch shipments with local storage and distribution managed by multiple partners

Advantages

- reduction of manpower expended by clinical team (import process, shipment monitoring)
- reduced risk of error leading to unnecessary clearance delays (fewer shipments/less potential for error or delay)
- flexibility in managing the distribution timeline
- better control of temperature and product quality
- reduced transport costs

Disadvantages

- complex chain of custody (pharmaceutical company/transporter/warehousing company/domestic transporter/investigator site)
- escalated risk associated with multiple partners
- need for additional in-country vendor qualification
- lack of clarity concerning roles and responsibilities

- potential for miscommunication
- potential for conflicting SOPs
- need for additional monitoring/intervention by clinical team
- cumbersome and time-consuming communications

COMPANY C

In-Country Warehousing Solution: 4 large batch shipments with local storage and distribution managed within a closed-loop supply chain system

Advantages

- reduction of manpower expended by the clinical team (import process, shipment monitoring, vendor qualification, redundancy of communications, problem resolution)
- reduced risk of error leading to unnecessary clearance delays (fewer shipments/less potential for error or delay)
- flexibility in managing the distribution timeline (in-country storage/distribution according to a pre-determined schedule)
- better control of product quality
- reduced transport costs
- efficient chain of custody (pharmaceutical company/logistics provider/investigator site)
- reduction of risk associated with multiple suppliers
- no need for additional in-country vendor qualification
- clarity of roles and responsibilities
- streamlined communications
- consistent SOPs
- no need for additional monitoring by clinical team
- a single contact or access point
- better opportunity to use structured QRM process thinking to master complexity and streamline decision-making
- improved transparency and QRM effectiveness to build trust with competent authorities

Selection Criteria for a Closed-Loop Supply Chain Provider

What are the key considerations in choosing a closed-loop supply chain provider? This question speaks directly to the infrastructure, experience and credibility of the provider. In answering this question, sponsors must be able to satisfactorily confirm the supplier's capability in each of the following areas:

- a gap-free service equation
- network-wide GxP compliance
- brick-and-mortar facilities in the country(ies) of interest
- experience and qualifications of staff
- integrated data systems

- ***True Full-Service Capabilities***

To qualify as a true closed-loop supply chain provider, the selected supplier must offer the full range of required logistics services in-house including:

- import/export/domestic transportation
- temperature-controlled storage facilities
- in-country distribution
- return/destruction of medications and supplies
- brokerage/customs clearance and/or support
- local regulatory support
- assistance in preparation of import/export documents
- local client support
- local temperature-control expertise
- validated and UN packaging and supplies
- active temperature monitoring and in-transit management capabilities
- dangerous goods expertise
- advancing of duties and taxes (as applicable)
- strong internal communications

For the integrated logistics provider and its clients, the weakest link in the chain is the one that is missing. With a full suite of services, the closed-loop supply chain provider can better support the sponsor's internal QRM requirements pursuant to ICH Q9 and provide necessary data to sustain objective decision-making.

- ***GxP Compliance***

In today's exacting regulatory environment, GxP compliance is the cornerstone of responsible biopharmaceutical research and product development. Virtually every international regulatory agency now calls for GxP compliance throughout the entire length of the clinical supply chain, applying its criteria to all third parties − both individuals and organizations − involved in any aspect of the pharmaceutical product distribution cycle including transport, storage and distribution. Ultimately it is the responsibility of the sponsor to ensure that suppliers comply with all applicable regulations including temperature control and product stability requirements. Penalties for non-compliance are severe and may include risk to public health, regulatory warnings, fines, declined new drug applications, and loss of partnerships and professional reputation.

Choosing a proven GxP-compliant logistical supply chain provider represents the “fast track” method of ensuring cold chain regulatory compliance from origin to destination. It ensures that all members of the logistics team are guided by identical SOPs and are subject to the same quality oversight. It also circumvents the need and expense associated with qualifying and auditing numerous vendors, and in doing so, streamlines the supply chain process while ensuring maximum quality and control. The selection of a GxP-compliant supply chain partner strengthens the QRM process, improves transparency within the study and enhances sponsor credibility with regulatory authorities.

- ***In-Country Infrastructure***

A high level of service consistency has never been more important than for clinical trial shipments destined for emerging markets. Sponsors should ensure that they understand the local service capabilities of their provider in *each individual country or market* where shipments will travel. Questions to consider include:

- will service be provided through company-owned offices or by sub-contracted agents?
- is the full-service offering outlined above available in all in-country locations as required?
- is there an in-country GMP-compliant, ISO-certified investigational drug storage facility?
- does it provide for all necessary temperature ranges including controlled ambient (15ºC to 25ºC), cold chamber (2ºC to 8ºC) and freezers (-15ºC to 25ºC).
- does it conform to the needs of the researchers?
- if storage facilities are not available, how are shipments handled?
- are suitable packaging materials and refrigerants readily available?

Sponsors should recognize that logistics providers offer varying degrees of geographical expertise. Companies with strong capabilities in specific countries in Asia Pacific, for instance, may not have the same proficiencies in Russia or Latin America. As such, sponsors should be certain to match the abilities of the service provider to the countries where the study is being conducted.

- ***Employee Qualifications***

Pharmaceutical transport and logistics has become increasingly complex and requires strong understanding on the part of those enlisted to deliver services. For many clinical trials, the front line is where the study succeeds or fails, making the training, expertise and ongoing qualification of logistics staff critical to ensuring the integrity of pharmaceutical shipments under their control.

On the transport side of the equation, customer service staff must have a strong knowledge of local regulatory requirements in all countries associated with the trial. They must be able to provide clear guidance in the preparation of import and export documentation to ensure that shipments are not unnecessarily delayed. Similarly their colleagues on the ground must have the experience and an established relationship with local customs in order to manage the timely clearance of incoming shipments.

The logistics team should also offer proven experience with dangerous goods as well as with all types of thermal packaging options including active systems, semi-active systems, passive systems, dry ice and liquid nitrogen shippers. They should be both willing and able to recommend appropriate packaging solutions capable of correctly maintaining the product within the desired temperature range for the duration of transit. Local operatives and drivers must be similarly trained in the pre-conditioning, safe handling, packing and replenishment of refrigerants as well as in correctly setting and downloading data recorders to deliver verifiable temperature data. Throughout transit all members of the logistics team must work in conjunction with established SOPs.

All investigational drug storage facilities should be staffed by qualified full-time pharmacists and trained logistics operators capable of managing incoming bulk shipments, the movement of materials to their assigned locations, and the collection and packaging of outgoing patient kits. Independent quality assurance specialists should also be in place in each location to monitor quality applications within the facility and ensure regulatory compliance.

Sponsors should not shy away from questioning the logistics provider's staffing capabilities in every country in which the study will be conducted and from learning how internal training is managed and how qualifications are maintained, especially in remote locations and/or emerging markets.

- ***Integrated Information Management***

Information technology plays a crucial role in enhancing communications between research partners in distant locations and across diverse time zones, in avoiding costly and avoidable transport errors that can disrupt a study, in streamlining processes and reducing time expended by the clinical team, and in managing clinical materials inventories around the world.

Sponsors should look for fully-integrated information systems that permit authorized users online access to up-to-date protocol details, shipment schedules and tracking capabilities as well as warehouse inventory management and stock control tools that ensure materials arriving or exiting a warehouse are fully traceable. A single entry system is optimal as it reduces both redundancy and the risk of error.

Conclusion

Today's marketplace offers many options for clinical trial transportation and logistics, reinforcing the need to evaluate both the sponsor's principle service objectives as well as those who will ultimately provide the services.

A single GxP-compliant supplier with a proprietary closed-loop clinical supply chain system − one that incorporates packaging, transportation, warehousing, customs brokerage support, logistics management, temperature-controlled management, documentation and centralized record-keeping − offers, without exception, the most straightforward solution for sponsors striving to consistently reduce risk and meet budgetary, regulatory and performance objectives. For the fully-integrated logistics supplier is truly the only organizational entity equipped to deliver a complete package of infrastructure, knowledge, expertise and process control in today's complex and often unpredictable international environment.

All other options represent piecemeal solutions aimed first and foremost at the theoretical reduction of costs, potentially (and albeit unwittingly) at the expense of overall performance and/or regulatory compliance. While price is undoubtedly an important consideration, economic advantage is short-lived if shipments are delayed or mishandled, if time is needlessly expended by the clinical team, if product quality fails, if dosing schedules are missed, or if ICH and other regulatory standards are not met.

About the Author

Dr. Rüdiger Lomb is Global Director, Quality & Technical Compliance for the World Courier group of companies. Since joining World Courier in 2008, Dr. Lomb has brought his considerable technical expertise to bear on shaping and refining the company's Quality Assurance program. Dr. Lomb was formerly Group Head and Director of the Global Logistics Clinical Supplies Division for Bayer Schering Pharma AG in Germany where he was responsible for the auditing and qualification of depot and transportation service providers. Dr. Lomb is a licensed pharmacist and holds a Ph.D. in pharmaceutical bio-chemistry.

www.worldcourier.com