Shipping with Active Packaging Containers

Three Pre-flight Decisions that Impact the Success of High-value Global Shipments

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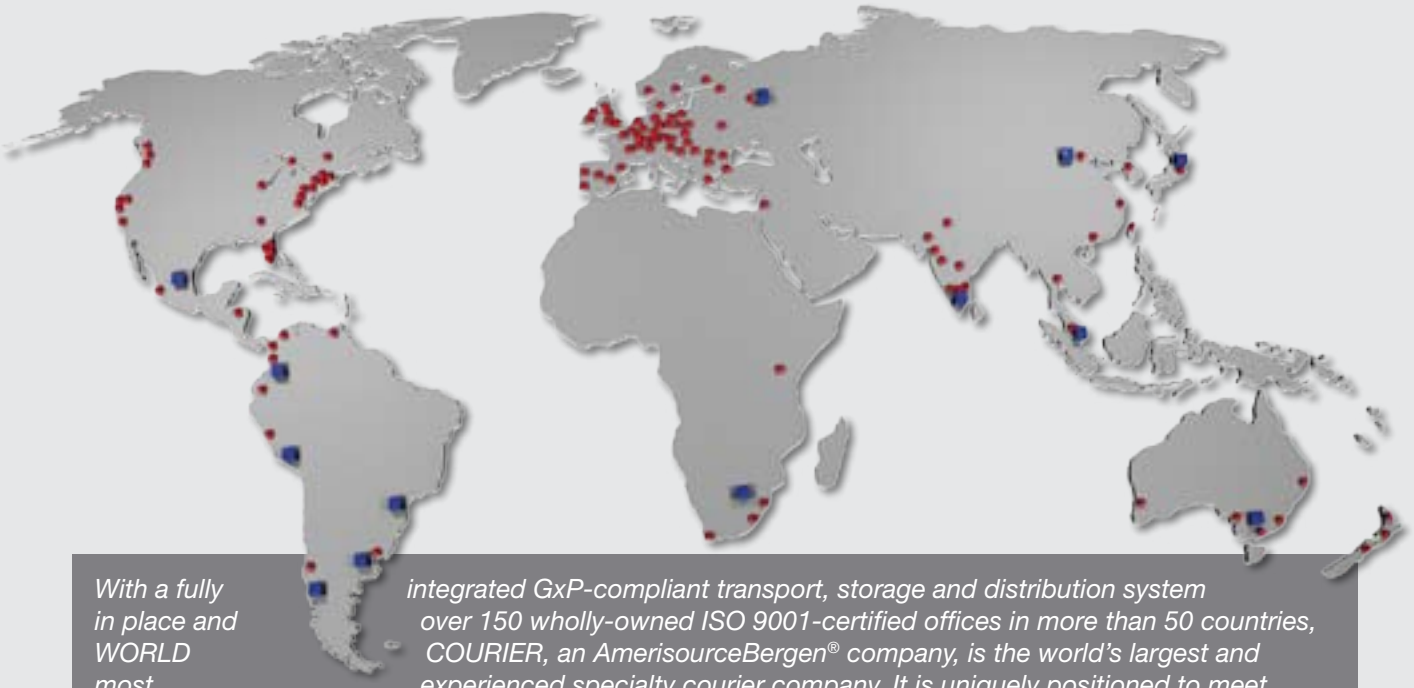

With a fully integrated GxP-compliant transport, storage and distribution system in place and over 150 wholly-owned ISO 9001-certified offices in more than 50 countries, WORLD COURIER, an AmerisourceBergen® company, is the world's largest and most experienced specialty courier company. It is uniquely positioned to meet the most demanding industry requirements for managing the global distribution of time- and temperature-sensitive pharmaceutical products and IMPs used commercially or in clinical trials.

It is the dead of winter in the northern hemisphere and the height of summer in the southern, with external temperature fluctuations exceeding 50 degrees. Flight delays have added precious days to the transport of your multi-million dollar shipment of blockbuster drug from South East Asia destined for Russia. In France, the roads are closed for days due to a monster snowstorm, with your irreplaceable shipment of investigational drugs stopped somewhere en route between Paris and the clinical trial site. Will all be lost, or can informed choices made before the shipment departs ensure product safety despite unforeseen circumstances?

The worldwide distribution of high-value temperature-controlled IMPs and pharmaceutical products presents significant challenge to shippers dedicated to ensuring product quality and patient safety.

From the selection of a packaging/container system to the choice of a logistics provider and its adherence to best transport practice, the wrong choices can result in significant product and financial loss, disrupt the supply chain and production schedules, expose the company to unnecessary risk and loss of reputation and ultimately jeopardize patient safety. This technical paper examines three key factors that can help shippers optimize global temperature-controlled pharmaceutical distribution.

Decision 1:

How can I optimize the cost-effective use of packaging and technology?

The Benefits of 'Active' Container Systems

Making the right packaging decisions are always the shipper's first priority, but never is this decision more important than for high-value shipments destined to far-off or emerging locations, or to locations known for a challenging import/regulatory environment.

'Active' packaging solutions offer reliable and mechanically-oriented temperature control for bulk shipments by using fans, thermostats, batteries and internal refrigeration/heating components to manage internal temperature. As the name suggests, active packaging systems are able to maintain the required temperature parameters of pharmaceutical shipments more independently than others. Available in a variety of sizes and models, these systems are proven to work effectively within specific temperature parameters and can be configured for temperatures ranging from -20°C to +30°C depending on the specific unit. Newer models continue to innovate by using compressors instead of dry ice bunkers to further improve technological reliability and reduce the amount of human intervention required. Over time these systems have become highly reliable and have been well proven in the field.

Some pharmaceutical companies have deemed active container systems to offer the highest degree of safety and have designated that all high value shipments be shipped using this type of packaging to meet internal risk management requirements. Why active container systems? Today's active units incorporate the most advanced temperature-controlled technologies currently available on the market. As a general rule and under most circumstances, shippers can expect most passive packaging qualification to expire in 48 to 96 hours. As the qualification period reaches its expiry limit, some packaging options may require a change of refrigerants or physical storage at the

correct product temperature in order to maintain temperature stability. The logistics of "topping up" refrigerants or securing appropriate temperature-controlled storage can present a significant challenge in many airports, especially those in emerging nations. In circumstances such as these, protracted customs clearance, flight delays or flight cancellations, lack of training or access to the container on the part of the logistics personnel can all potentially put the stability of the shipment at risk. Conversely, the newest models of active unit need only be plugged in for recharging to extend the qualification time.

EXTENDING QUALIFICATION TIME

Perhaps one of the clearest-cut criteria to support the decision to use an active container unit relates to the expected transit time. As stated above, most passive packaging qualification expires within 48 to 96 hours – in essence permitting a total time expenditure of just two to four days to successfully

pack the contents, pick up the shipment, manage security clearance, lodge with the airline, transport from origin to destination, negotiate any secondary transit points, obtain customs clearance, recover from the airline and deliver.

Despite good planning, contingencies can and do occur: flights may be delayed or cancelled, airports or roads closed due to weather, customs inspections or customs delays incurred, or deliveries hampered by strikes or other civic actions. For any high-value shipment containing a temperature-sensitive commodity, risk mitigation may be best achieved by using an active container unit where any delay – no matter how long – can be effectively managed by simply having access to a source of electricity.

COST

Another benefit of using active container units can be the potential cost savings derived from transporting a lower weight shipment. Particularly in the case of Heat/Cool units which rely on compressors rather than dry ice, the lack of refrigerants may significantly reduce weight and hence, shipping costs.

Shippers should consult with their Quality Assurance department to determine if such an internal policy exists, particularly when distributing expensive temperature-controlled commercial or specialty products with high unit value or low production volumes, or other types of compounds or therapies which may possess a high intrinsic value. The latter could include investigational drugs or even placebos for which a compromised product could result in a clinical trial being halted or the quality of research results being called into question.

Assuming the decision has been made to use an active container unit, how does the pharmaceutical shipper determine the right active packaging unit for a shipment?

SHIPMENT SIZE

The size of the actual shipment – known in transport terms as the 'payload' of the shipment – will, in some cases, determine the appropriate choice of container system or, indeed, the actual active unit chosen. While other packaging systems may be limited to shipments of a single pallet or less, active systems have essentially been designed to accommodate larger consignments, with some of today's models able to accommodate multiple pallets. For this reason, active systems are often the first choice for the transporting of high-value bulk shipments.

Active units are currently produced by three major manufacturers: Envirotainer, Lufthansa and CSafe. Envirotainer and Lufthansa each produce two basic sizes: the RKN model, which holds up to one pallet (U.S. or Euro) and the RAP model, which accommodates up to four U.S. pallets/five Euro pallets. CSafe currently offers only the RKN model (one pallet). With each manufacturer/model offering slightly different product features, a skilled logistics provider can choose the exact make and model best suited for a specific shipment.

No minimum payload size exists on the lower end, so shippers may transport even the most minute product quantity in an active container.

TEMPERATURE/PRODUCT STABILITY REQUIREMENTS

Assuming that the decision to use an active unit has been made, exactly which model is most appropriate? There are currently three different technologies on the market: Cool Only, Heat/Cool using dry ice and Heat/Cool using a compressor. The Cool Only units utilize dry ice to maintain lower internal temperatures in the -20°C to +20°C range. Alternately Heat/Cool units – which are typically used to maintain temperatures in the 0°C to 30°C range – incorporate a heating/cooling unit within the system to maintain temperature while relying on a bunker of dry ice as the cooling medium. Other newer systems like Envirotainer's RKN e1 and RAP e2 and the CSafe RKN utilize electric heating and compressor cooling (rather than dry ice) to maintain lower temperatures.

Because the stability of active pharmaceutical products or compounds can be negatively influenced by environmental conditions including temperature, air, humidity or light, the long-term reliability of the active container can provide added insurance in most contingencies. Data is available from the manufacturer attesting to unit performance.

As discussed above under payloads, the design of each active unit varies by manufacturer and accommodates a slightly different temperature range. Once again, an experienced logistics provider can provide guidance on the most appropriate choice of unit based on the shipper's temperature requirements.

TRANSPORT CONSIDERATIONS
Beyond temperature requirements, the final destination of the shipment and its proposed routing play a particularly critical role in selecting the proper active container unit. There are three important reasons – one is regulatory; the second, proprietary; and the third relates to simple airline/airport logistics.

REGULATORY/PROPRIETARY | Generally speaking, all makes of active units are not accepted by all airlines.

- Envirotainer Heat/Cool units, for instance, are not FAA-approved and, as such, cannot travel on U.S. carriers. Cool Only units, however, can be accepted.
- CSafe units can travel on any airline, provided the individual airline has approved their use. Major airlines currently accepting CSafe units include, but are not limited to, US Airways, United Airlines, British Airways, Air France, Air Canada, KLM, Japan Airlines and SwissAir.
- Lufthansa units can travel only on Lufthansa flights.

Clearly the final destination and the routing selected by the logistics provider – in conjunction with shipment size and temperature requirements – will largely determine the actual choice of active unit.

AIRLINE/AIRPORT LOGISTICS | While logistics providers typically forward pharmaceutical shipments on the most direct route to reduce the potential for flight delays/missed connections and to deliver as expeditiously as possible, transport options may be further complicated by the equipment used by the airline and/or by national airport policy.

Because of their size, active units can only be shipped on wide-body aircraft, making routing decisions even more complex. Wide-body aircraft are typically used only on longer-haul or inter-continental routes, so intra-European shipments, for instance, may require additional consideration. In these cases, logistics providers may choose high quality temperature-controlled ground transport services instead to expedite bulk deliveries. In other cases, such as between the U.S. and Mexico where wide-body aircraft are not utilized, transport decisions can become highly creative with routings designed via an international point in Europe or Latin America to accommodate the use of active containers.

Adding another twist to delivery in certain destinations are national airport restrictions that prohibit active units from being removed from the airport premises. In countries like India and Russia, for instance, where such restrictions apply, logistics providers must ensure that appropriately-sized temperature controlled vehicles are in place to retrieve unit contents and manage the delivery.

Clearly, while the choice of active unit may alleviate specific issues, their use can create challenges in other areas.

Decision 2:

How can I mitigate risks and human error?

Although today's active container systems are perhaps more reliable than at any time in the past, they still require human management and intervention to ensure a successful delivery. The individuals handling these units – whether at the point of origin, destination, or at transfer points in between – must have a strong working knowledge of the unit's function and operation as well as fully understand Good Distribution Practice (GDP) as it applies to the use of the container during transport. They must also ensure that the proper SOPs are followed with respect to the qualification of the unit, during security screening and while implementing recovery measures in the event of an unexpected failure.

PRE-QUALIFICATION SOPS

Renting active units on an ad hoc basis from the manufacturer, logistics providers should routinely test each unit for temperature accuracy prior to delivery to the client for packing. This basic testing – which can be as simple as storing a bottle of water in the unit with a temperature monitor for 12 hours – will immediately confirm whether the unit is correctly calibrated to interior air temperature readings. In the event that a unit fails this qualification test, it should be returned to the manufacturer and the process reinitiated with a replacement unit. Understanding the logistics provider's standard qualification procedures before pick-up may be the easiest way to circumvent up-front equipment failures and unnecessary delays.

SECURITY SCREENING/AIRLINE COMMUNICATION

Some logistics providers are authorized by local transport regulators to perform in-house security screening after the unit has been packed/closed by the shipper and prior to check-in with the airline. Designed to streamline the loading of verified cargo onto passenger aircraft, this is known as the Certified Cargo Screening Program (CCSP) in the U.S. Similar programs exist in the European Union which allow regulated agents to perform approved security measures for air freight screening and in other countries like Canada (Air Cargo Security

Program). This capability can help reduce the lead-time required between pick-up and check-in with the airline, potentially preventing missed close-outs and/or flights. In such cases, logistics personnel will perform prescribed testing which usually makes it unnecessary for the airline to re-screen at check-in.

Logistics staff also ensure that units are clearly marked “Customer-loaded. Do not open” to prevent unnecessary entry, manage all airline communications and reconfirm that labeling, documentation and storage instructions are clear and complete. Some providers may even ensure that all airline documentation appears in the language of the country of destination to further eliminate the potential for error.

The hand-off of the shipment between logistics provider and airline is one of only a few instances when chain-of-custody is transferred. Shippers should ensure that logistics personnel are fully informed of proper procedures and able to execute consistently and accurately.

TRAINING & ACCREDITATION

Because of the high-value nature of goods typically shipped in active containers, manufacturers have programs in place to ensure the reliability of the unit. In the case of Envirotainer and CSafe, each relies on logistics providers trained in the basic operation, handling and maintenance of their units to act as local agents in handling and, when necessary, to trouble-shoot any minor malfunctions that might occur.

Through its Qualified Envirotainer Program (QEP), Envirotainer offers accreditation to transport/logistics providers who are able to properly manage shipments using their equipment while meeting industry driven GDP guidelines such as IATA’s Perishable Cargo Regulations. Similarly, CSafe’s Enhanced Qualified User Program (EQUiP®) recognizes cold chain logistics providers whose staff have met training and assessment criteria for handling their containers and meet global compliance requirements. Unlike its competitors and, perhaps due to the availability of its own airport personnel, Lufthansa manages all maintenance of its proprietary units locally rather than provide specific training to external service providers.

Pharmaceutical shippers should ensure that their logistics provider is adequately trained and certified as required to manage any consignments housed in active containers. Service provider staff should be accredited not only at the point of origin, but more importantly at the shipment’s destination and at all transit points in between. The availability of back-up units in the event replacement is required should also be assessed at all points during transit.

Decision 3:

Beyond price, what should I evaluate in transportation partners?

In the global distribution of high-value IMPs and pharmaceuticals, choosing the right logistics provider represents a crucial decision in securing the supply chain. What types of credentials should your provider offer? What types of questions should they be prepared to answer?

ORGANIZATIONAL CAPABILITIES
- What type of experience does the logistics provider have with temperature-controlled shipments? With active units?
- What is the logistics provider's track record with these types of shipments?
- What type of reputation does the provider have with airlines? Customs? Other pharmaceutical shippers?
- Can he "think outside the box"?
- What is the scope of the provider's global network?

TRAINING & ACCREDITATION
- Are staff in all transit locations (not just origin/destination) adequately trained to handle, manage, trouble-shoot active unit shipments?
- Are staff accredited by the manufacturer under the QEP (Envirotainer) and/or EQUiP® (CSafe) unit maintenance programs?
- Is training documented and routinely updated?

SCREENING/SECURITY
- Is the logistics provider able to pre-screen shipments in a secure facility?
- Are SOPs in place for shipments that have been successfully screened? For those that fail?

IN-TRANSIT CAPABILITIES
- Can active units be proactively managed while in transit (temperature-monitoring, battery/dry ice replacement, other intervention)?
- Are in-transit personnel employed or sub-contracted by the logistics provider?
- Do local staff have the required expertise to intervene as needed? To access the shipment in secure areas?

FOLLOW-UP & FEEDBACK
- What procedures come into play in the event of a temperature excursion?
- How are excursions reported/investigated?

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A Final Word on Active Containers

Today's active container unit represents the next generation of pharmaceutical packaging standards. Key benefits include unprecedented independent temperature reliability, large payload capacity and product stability over long spans of time and distance, making the active unit the ideal packaging choice for bulk high-value pharmaceutical products and IMPs.

History has proven that the active container can withstand dramatic fluctuations in external temperatures, successfully navigating routings from India in the heat of summer, to Russia in the dead of winter and can keep contents protected during virtually any unforeseen circumstance, including customs/flight delays and major weather events.

Despite the innate reliability of the units, shippers should bear in mind that these containers are still inanimate objects that require handling, managing and intervention by skilled logistics providers. Although many shipments will arrive successfully at their destinations in the absence of professional oversight thanks to the meticulous engineering of the unit, some will not. As a shipper, are you willing to risk that the one that fails is carrying your multi-million dollar shipment of blockbuster drug or an irreplaceable IMP that can bring your study to a halt?

Patty Santopadre *is Manager of the Active Systems Team for World Courier Inc. (USA), an AmerisourceBergen® company. Patty is a primary resource throughout the company network for the handling of active systems and plays an integral role in shaping policy for the use of these systems globally. She has been with World Courier for 14 years and has over 34 years of air transport experience.*

[i] *(Air Carrier Security Program: Commission Regulation (EU) No. 300/2008; Commission Regulation (EU) No. 185/2010)*