

Time- and Temperature-Controlled Transport: Supply Chain Challenges and Solutions

Claire Sykes

What grocery store would sell unrefrigerated meat or outdated cartons of milk? Yet, across the globe, billions of dollars worth of pharmaceutical products are stored and shipped at improper temperatures, or they're delayed so they reach their destinations past their shelf lives.^{1,2} Such incidents make some drugs not only ineffective, but harmful and possibly even life-threatening to the people who count on them for everything from preventing the flu to fighting cancer.^{3,4}

It's not as if pharmaceutical companies and other industry stakeholders don't know or care about this problem. But, as they maintain good distribution practices, they face challenges with the supply chain's complexity of environments, from drug manufacturer to wholesaler to hospital or clinic to patient. So many hands packing, lifting, hauling, and delivering products can leave room for human error. Preventive and corrective measures can be expensive, too. Add in complicated government and other regulations, and the pharmaceutical industry must surmount an array of hurdles.^{3,4}

When drugs are improperly packaged, stored, or shipped, damage to them—or, worse yet, to patients—means potential damage to the pharmaceutical companies. Along with subpar and spoiled products can come lawsuits and public relations nightmares, tarnished reputations, and shareholder distrust that cost companies more than dollars.⁵

But breakthroughs in therapeutics research, technologies, and logistics are supporting continued progress in the pharmaceutical supply chain: packaging innovations, tracking and monitoring advancements, warehouse upgrades, shipping and transportation improvements, educational and training programs, and policy and regulatory development. Bioscience researchers are even looking to the molecular level of drug manufacturing for answers to temperature-control questions. Moved by stricter regulations in Europe, the United States is tightening its rules to sharpen its competitive edge.

The Risks Aboard

The term “cold chain” for uninterrupted refrigeration has given way to “temperature-controlled.” The spectrum ranges from ambient, or controlled room temperature (20°C to 25°C), to refrigerated (2°C to 8°C), to cryogenic (below 0°C to as low as -150°C).^{3,4,6} *Pharmaceutical & Medical Packaging News* surveyed supply chain experts in 2015 and arrived at these findings: Of temperature-sensitive products shipped, 51% were ambient, 31% were refrigerated, 17% were frozen, and 32% should not be allowed to freeze.⁷

Many pharmaceuticals also react to humidity, light, vibration, and shocks.⁵ The key for radioactive therapeutic agents is half-life, the time it takes an isotope's radioactivity to decrease by half of its original value, thereby losing its potency. For some drugs, that's just a matter of days.⁸

More types and numbers of drugs are sensitive to temperature or time than ever. That's because drug research and development are evolving past traditional chemical-based, small-molecule therapeutics to more complex and often more effective large-molecule biologics.^{3,4}

What can damage these drugs? Perhaps they're exposed to the elements for too long because of delays, packaging failure, or incorrect handling. Cold air or hot breezes, cold and hot times of day, and intensity of sunlight can hit products with temperatures they can't withstand.² Freezing some liquid drugs, such as insulins, can compromise their integrity if they're then quickly thawed. Freezing also can negatively impact solid forms of some drugs.⁵

The number of pharmaceutical products harmed by incorrect timing and temperature is difficult to pinpoint. Generally, the earlier pharmaceuticals sit in the supply chain, the greater the control, says Henry Ames, General Manager of Life Sciences at Sensitech, Inc. Based in Beverly, Massachusetts, Sensitech is one of the world's leading providers of supply chain visibility solutions focused on monitoring and protecting the integrity of temperature-sensitive products in the food, life sciences, and industrial markets. “For example, temperature management for pharmaceuticals is based on adhering to label claim throughout storage and distribution. Label claim is based on stability data, determined by the manufacturer, which sets the total time-out-of-refrigeration ‘clock’ for maximizing product efficacy. As products begin their journey through the supply chain, the manufacturer ‘starts the clock’ by shipping full trailers of the same label-claim product. When the products reach wholesalers, who might not have received the stability data from the manufacturer, pallets are broken up and products are comingled for distribution with other products, and those products' label claims could be a mixed bag. Distribution at this stage from the wholesaler is more complicated and costly from a temperature-management standpoint,” Ames says.

“The deeper you go into the pharmaceutical supply chain, the less control is exhibited and the less investment is made to ensure proper storage, handling, and distribution,” Ames adds. “Similarly, there is less oversight and auditing by the various regulatory agencies and state boards of pharmacy, when compared with earlier stages of drug distribution.”

The consequences of problems can be potentially life-threatening. In August 2017, for instance, a shipment from a single lot of Intralipid 20% IV fat emulsion, 100 mL bags (Baxter International, Inc.), was improperly exposed to subfreezing temperatures—those outside the labeled acceptable storage range—on its way to a distribution facility. The company voluntarily recalled this parenteral-nutrition product about two months later, and warned patients to dispose of their supplies. When frozen, the product's emulsion droplets enlarge, forming aggregates that can obstruct pulmonary circulation, leading to serious health problems and possible death.⁹

Claire Sykes is a freelance writer based in Portland, Oregon.

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For some solid drugs, if they're not packed tightly enough, humidity can alter their characteristics. And if they're naturally friable, vibrations and shocks could damage them.³

Counterfeit drugs can also slip into the supply chain, and more than half of the top 32 counterfeited drugs have strict temperature-control logistical requirements. Some liquid forms are easy to dilute, making them as ineffective and possibly just as dangerous as a product that has experienced temperature excursions. Counterfeits of still-branded medications can fetch especially high dollar amounts.⁵

"While we enjoy a relatively low level of counterfeits in the U.S., increased Internet use and global delivery of products in the traditional supply chain have increased the risk here," says Scott Mooney, Vice President of Distribution Operations at McKesson U.S. Pharmaceutical. It's easy for patients to order many pharmaceuticals online, but not knowing the seller and having only a photo of the product, there's a chance the drug could be a fake.

Radioactive drugs aren't likely to be counterfeited. Instead, their inherent hazard lies in active ingredients that sport half-lives. Consider Bayer HealthCare Pharmaceuticals' FDA-approved Xofigo injection (radium Ra 223 dichloride), formerly known as Alpharadin. It's one of the first alpha-particle-emitting radioactive agents (those with a high relative biological effectiveness) to treat men with castration-resistant prostate cancer, as well as symptomatic bone metastases, who have no known visceral metastatic disease. The drug, which emits radiation at the site of bone metastases, exerting an antitumor effect, aids patients who want to avoid chemotherapy and its side effects.⁸

The total shelf life of radium 223 is roughly four weeks, and its half-life is about 11 days. "From the moment an order is placed, Xofigo must be manufactured, transported, properly dosed, and delivered to the customer within the 28-day window, otherwise it becomes ineffective, and expired product should not be administered to patients," says Joseph Germino, MD, PhD, Bayer's Vice President of Medical Affairs for Oncology. Xofigo was previously manufactured only at one central location, in Oslo, Norway. In 2017 Bayer opened a state-of-the-art manufacturing facility in Indianapolis, Indiana, operated by Cardinal Health and dedicated exclusively to Xofigo for the U.S. and Canada. "Now we can streamline our production and distribution of it—performed according to high industry standards—and ensure sufficient and safe supply," Dr. Germino says.

Getting Educated and Regulated

Pharmaceutical companies everywhere can do the same by taking a holistic approach to their supply chain logistics. It starts with a designated logistics team. Clearly defined standard operating procedures, rooted in thorough risk assessment, form the foundation to take action—before the product enters the supply chain. The newest on-board and back-end information technology pinpoints environmental conditions, monitors temperature and time, and strengthens security.^{2,4,6}

Then there's education. "Too many pharmacy education programs fail to teach the details of temperature-controlled logistics management and its importance for efficacy to the patient," says Mark Maurice, Professional Services Senior Project Manager in Life Sciences at Sensitech. "When in doubt, pharmacists should seek expert advice in this area." Wholesalers can also

hire third-party logistics (3PL) firms, such as UPS or FedEx, to act as their agent in handling everything from order fulfillment and payment to product distribution and delivery. A 3PL firm can provide more flexible packaging and transportation solutions and risk-management options.⁴

This can help maintain rigid adherence to regulatory standards set by the International Air Transportation Association (IATA), U.S. Department of Transportation, Transportation Security Administration, U.S. Customs and Border Protection, and the FDA's current good manufacturing processes. An IATA Standard Acceptance Checklist for airlines, in the sky and on the ground, makes sure temperature-sensitive shipments meet all temperature control regulation requirements. However, U.S. regulatory agencies, unlike those in the European Union, Canada, and other countries, limit their focus to distribution.

"The FDA regulates wholesalers and points to two key elements when auditing: the Interstate Commerce Act and the FDA's definition of the word 'holding.' Holding occurs when a drug is distributed, transported, or warehoused for distribution or transfer," Maurice says. Ames adds, "Regulatory agencies have historically focused on biologic products (typically stored at 2–8°C). The rational risk-based approach naturally guides regulations and auditors toward those products treating the most critical and life-threatening circumstances. That said, the market has evolved, and the regulations do not distinguish between products stored at different temperature ranges. Strictly speaking, a product is considered adulterated when stored outside of its published label claim, regardless of the temperature range. In the past few years, there has been increased attention placed on products that would largely fall into the category of controlled-room temperature."

In an effort to prevent illicit drugs from entering the supply chain, Congress passed the Drug Supply Chain Security Act (DSCSA) in 2013; requirements began to take effect in 2015. The DSCSA requires consistent licensing and sales-transaction data to prove legality.¹⁰ "McKesson has a long-time policy of purchasing pharmaceutical products direct from the manufacturer, its exclusive distributor, or a repackager who purchased direct," Mooney says. "This keeps our supply chains short, with known trading partners, and adds a level of integrity. We only obtain a product from the same consistent source where we've established a relationship. This is then supported with those trading partners providing us with DSCSA transaction documentation, prior to the acceptance of any pharmaceuticals into our inventory."

Packing It Up

Pharmaceuticals with temperature-sensitive and shelf-life concerns deserve the most experienced, extensive, and expedient shipping attention. But that doesn't assure quality and safety unless products are packed correctly. "The responsibility lies with the pharmaceutical shippers to ensure appropriate packaging," says Andrea Gruber, Senior Manager of Special Cargo with IATA.

Again, from *Pharmaceutical & Medical Packaging News's* 2015 survey of temperature-sensitive supply chain experts: One-third of companies make packaging a top priority. But only about one-fifth are aware of the environmental conditions under which their shipments travel; without this, they can't

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know how to package them most effectively. It's not surprising that the proportion who have created scientifically customized packaging systems is just as small. An expert audit is the best way to know if those systems are working, and just less than half of respondents said they had no intention of seeking those services.⁷

Pharmaceutical companies tend to either overengineer or underengineer packaging. There are two types—active and passive. Active ranges from a separate, individual package and full container to entire trailers and aircraft. Since active packaging relies on its own thermostatic-controlled energy source, the outside temperature generally doesn't affect products. But external conditions can affect passive packaging, which uses conventional packaging combined with wet ice, gel packs, dry ice, or liquid nitrogen (LN₂), depending on the temperature control needed.⁴

The choice of active or passive packaging comes down to a risk-benefit balance.³ Making the passive-packaging choice may be easier with the latest technology. The newest analytical thermal modeling tools can offer greater understanding in the way temperature behaves inside a given space; advanced phase-change materials (PCMs) put that understanding to optimal use. Frozen and then while melting as internal temperatures rise, naturally or otherwise, during the day, PCMs absorb heat energy that they later release as those temperatures fall. When designed to meet that environment, PCMs result in a relatively consistent, desired temperature. An improvement over water-based packaging and previous PCM varieties, the newest ones use less-costly polyurethane and polystyrene insulation substances. They accommodate smaller, lighter packaging and can be reused, reducing the carbon footprint—and packaging price.¹¹

Any packaging should be tested, in the lab and the field, first for distribution stresses, such as vibrations and drops, and then for temperature influences.² However, even the strongest, most appropriate material or method will fail if the packaging is not handled properly. Specific freight-forwarding instructions regarding government and other regulations, temperature sensitivity, shelf-life considerations, and transportation conditions can prevent miscommunications that can lead to compromised product quality.²

For temperature-controlled freight, the pharmaceutical company is responsible for proper shipment labeling. A label's pictograms indicate a package's temperature-control requirements and physical orientation ("This side up"), particularly important for LN₂ packaging and containers. Mandatory since July 2012 and specific to the health care industry, the IATA Time and Temperature Sensitive Label, which gives the shipment's external-temperature range, must be attached to such cargo.¹²

"The continued rollout of the DSCSA is perhaps the most critical piece at the moment, as the U.S. changes the way we identify pharmaceuticals," says McKesson's Mooney. "Moving from a linear bar code to a two-dimensional data-matrix bar code—which encodes the product's identifying National Drug Code number, the lot number, expiration date, and serial number for a package—will provide some huge benefits to the supply chain. For temperature-sensitive products, this additional information can help manage product rotation, increase visibility regarding products entering and leaving the supply chain, and confirm

that the product has not expired. Using these new bar codes and traceability under the DSCSA, we can begin to assemble the history of a particular product's location in the supply chain. Then we can piece together the temperature conditions a product was stored under, and for how long."

Moving Through the Chain

Many more pharmaceuticals are traversing the roads, rails, and skies. Risks of error and failure await. Routes can be long and complex. Exchanges and drop-offs may require many modes of transportation and points of communication. Bad weather can bog down transit. So can hangar and dock delays, with shipments waiting in a plane or ship that's too cold or sunlight that's too hot.⁵

IATA has recognized the air transportation industry's effort to address pharmaceutical manufacturers' needs by developing a new initiative, the Centre of Excellence for Independent Validators in Pharmaceutical Logistics (CEIV Pharma).¹³ "This globally recognized and standardized certification for pharmaceutical air shipments ensures that the right processes, people, and infrastructure are in place to handle and transport sensitive shipments in compliance with existing international and national regulatory requirements," Gruber says. Supply chain stakeholders can voluntarily be assessed and validated by IATA to receive the certification.

In August 2017, Delta Cargo became the first U.S. global passenger carrier to achieve this mark, applied to its headquarters and largest hub in Atlanta, Georgia, with more hubs expected. Delta can connect shipments from there to the seven (so far) CEIV Pharma-certified entities in Europe. In conjunction with the certification, Delta launched its active Envirotainer RAP e2, which adds to the passive insulated containers using dry ice and/or PCMs to control temperatures. "These newest containers are a very secure, safe, and reliable way to move pharmaceutical cargo sensitive to time and temperature. They're above and beyond what certification requires, but it's the right thing to do for critical pharma shipments," says Julian Soell, Managing Director of Operations and Customer Experience at Delta Cargo in Atlanta. Delta also added greater quality control with specified policies, procedures, and training for pharmaceutical requirements, supported by a quality-management system that seeks out and addresses concerns.

Communication and transparency are key "when cargo gets transferred between different stakeholders across the supply chain," says Gruber, who stresses a collaborative approach. "This helps clarify expectations from the outset, and minimize the risks and challenges for air freight within the supply chain. It also results in air-freight stakeholders having a better understanding of the concerns of pharmaceutical companies and the complexities occurring in the logistics chain. These actions help mitigate the potential risk of temperature excursions throughout the journey."

Keeping Track to Stay on Track

The last thing anyone wants is a package delivered after the expiration date, or a crate with frozen gel packs that slipped off their perch on the product in transit, raising a risk of overheating. Worse, what if no one notices until the product has reached its destination, when it's too late to do anything about

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it?²² Monitoring temperature and timing of shipments along the supply chain confirms compliance as much as it detects weaknesses and errors, almost as soon as they happen and before they become systemic.

Perhaps interventions are called for right then: Reroute that shipment, reposition shifted packages, or readjust temperatures. Along with individual shipments, today's sophisticated monitoring programs assess distribution as a process—over time and in real time—helping to distinguish between unexpected events and predictable trends. The collected data can be used to inform needed changes, improve quality control, meet regulatory requirements, and reduce costs.

Before products set off for their destinations, they may first sit in storage. UPS's 50 health care-dedicated facilities around the globe, certified to local and state standards, provide a variety of temperature-controlled options. "Layered on top of our warehousing and storage solutions are quality-assurance and product-protection services that mitigate spoilage and embody our 'it's a patient, not a package' mantra," says David Hoeller, Marketing Manager of UPS Global Logistics and Distribution Team. UPS offers four "Temperature True" options for temperature-sensitive air and ocean freight, all with proactive monitoring and intervention services.

FedEx's Temp-Assure portfolio—from deep-frozen to cold to controlled-room—maintains pharmaceutical products at consistent, required temperatures. When bad weather delays a shipment, the company can move it into in-transit, temperature-controlled storage. The company's SenseAware, a real-time, sensor-based monitoring system, indicates whether a shipment has been opened or subjected to light, humidity, or sudden movement. It also tracks the entire supply chain.

In preparation for CEIV Pharma certification, Delta Cargo equipped its warehouses with temperature-calibrated coolers, using thermal mapping to assure temperature consistency throughout. In any physical space, temperatures can vary near air vents, open doors, heaters, and fans. Thermal mapping, necessary to acquire qualification certification, records those temperatures and its fluctuations, three dimensionally—in the top, bottom, sides, and middle of a storage room, container, or vehicle.

Sensitech's full-service Thermal Mapping Services and self-administered Thermal Mapping Kits seasonally assess shipping lanes. Throughout McKesson's facilities, radio frequency identification data (RFID) provides real-time monitoring and tracking. Temperature and humidity sensors, linked to the company's computer systems, record problems, should they occur. "If so, the system alerts local management that the space is moving out of compliance, so we can implement established back-up plans," Mooney says.

Advancements Ahead

Thoughts of those back-ups likely never occur to patients; what matters to them is their health. And to optimize their health, what matters most to pharmaceutical companies is quality control and compliance. Companies that keep a competitive edge stay abreast of compliance developments. Whatever their place in the supply chain, they constantly look for ways to innovate.

So does the life sciences industry. StoneStable, Inc., a Portland, Oregon-based start-up connected with Portland State University (PSU), is seeking to "revolutionize" the transport

of vaccines. It's experimenting with coating viruses in silica, rendering them inert and impervious to hot and cold temperatures, and then later returning them unharmed to their original state. The company is in the first phase of testing the process with the influenza vaccine.

"On the molecular level, we're working at building a kind of 'nanofridge' around a drug particle, to prevent it from becoming inactive," says virologist Ken Stedman, PhD, Founder of StoneStable and Professor at PSU. "The pharmaceutical company would integrate these particles, our proprietary technology, into its existing drug-manufacturing process. This would remove refrigeration from the equation and allow the vaccine to survive at room temperature. When it's injected into the patient, the silica would dissolve in the bloodstream, and [the vaccine would] take effect."

In another lab 3,000 miles away, Vaxess Technologies, based in the Harvard Life Lab in Boston, Massachusetts, is looking to silkworms to help alter the behavior of vaccine molecules and save these drugs from degradation when left at room temperature or higher. Two things happen when heat and vaccines meet: It causes charge-based interactions that make the molecules stick together; and it denatures the vaccine antigen, thereby changing the molecular structure.

Vaxess began with the strong yet flexible fiber that the silkworm makes from the protein solution it extrudes through a gland. "We broke that fiber back down in a protein solution and turned it into different materials with unique properties. These are capable of entrapping the vaccine molecules so they can't move around and stick to each other, or change," says Michael Schrader, Co-founder and CEO.

Innovations such as these, as well as other drugs, may soon routinely travel by drone to reach destinations quickly. This would especially benefit people in disaster, weather-stricken, and rural areas; war zones; and third-world countries. In September 2017, Timothy Amukele, MD, PhD, Assistant Professor of Pathology at Johns Hopkins University School of Medicine, and Jeff Street, a drone engineer there, set a medical-drone-delivery distance record of 161 miles in three hours across the Arizona desert. Blood samples, kept at an average of 24.8°C inside the drone's refrigerator, remained viable.

For the pharmaceutical industry, Dr. Amukele says, "I'm convinced that drones really are the future because they can go where other vehicles can't, and their prices are reasonable. They may not be flying today, but they will be in a few years. It's not a maybe. So get ready."

As science continues to venture into new territory, the time- and temperature-controlled supply chain will drop links that weaken it and add new ones that strengthen it. Along the way, research and attention to quality promise to fortify that chain, benefiting those who depend on it the most—patients.

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