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THE SMARTER COLD CHAIN:

FOUR ESSENTIALS EVERY COMPANY SHOULD ADOPT

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THE SMARTER COLD CHAIN: **FOUR ESSENTIALS EVERY COMPANY SHOULD ADOPT**

Ensuring product integrity and security throughout the supply chain has always been a high priority for life sciences and healthcare manufacturers. However, a convergence of new forces – a changing product portfolio, stricter regulations, extended geographic coverage, increasing risk and intense cost pressure – is significantly raising the stakes.

Pharmaceutical manufacturers face an exponential growth in the need for temperature assured distribution and handling of materials, from active ingredients to finished products. This stems, in part, from a dramatic change in the nature of pharmaceutical and biotechnology products. Drug portfolios are evolving away from primary reliance on small molecule/chemical pharmaceuticals, toward more structurally complex biotechnology drugs, which often have much stricter temperature requirements. In addition, new regulations and expansion into new geographies are driving substantial growth in the requirement for controlled ambient (15 to 25°C) handling of products.

"Gaps and breakdowns in good [distribution] practices can trigger a chain of dire consequences for manufacturers – from increased regulatory scrutiny and steep financial penalties to slumping sales, a surge in shareholder apprehension, an irreversibly damaged brand and reputation, and worst of all, compromised patient safety," say Jamie T. Hintlian and Ryan Kelly of consulting firm EY. "Companies that have had a supply chain disruption have seen their stock prices fall by as much as 9 percent."[1]

[1] Jamie T. Hintlian and Ryan Kelly, "A Roadmap for Risky Territory," Ernst & Young, 2014.

WHY IS HAVING A SMARTER TEMPERATURE-CONTROLLED SUPPLY CHAIN SO IMPORTANT?

CONSIDER THIS SCENARIO:

Situation:

A pharmaceutical manufacturer was entering a new market with its breakthrough oncology drug. The product, which requires a temperature range of 2 to 8°C, is manufactured in France. The manufacturer was shipping its first consignment, valued at €2 million to its distribution center located in Chicago, USA.

Problem:

The manufacturer assumed its third party logistics provider (3PL) understood the handling requirements of the product. Unfortunately, that was not the case. The manufacturer had selected a passive packaging solution that was approved to protect the shipment for 96 hours. The 3PL booked the load as general cargo from Paris Charles De Gaulle Airport to Chicago O'Hare Airport, where the January outside temperature was -10°C. Based on the 3PL's booking neither the airline nor the airport handling facility knew about the product's temperature requirements, and the shipment was subsequently exposed to extreme temperature conditions. Additionally the door-to-door transit time was 135 hours, far exceeding the qualification period of the packaging solution.

Upon receipt of the shipment, the distribution center's Quality Assurance (QA) department reviewed the data loggers' information and identified a number of temperature excursions for the product during transit. They immediately requested a corrective & preventive action report, and placed the product under quarantine while the investigation took place.

The investigation took two weeks and identified several deviations in temperature between origin airport and destination. Stability data suggested these excursions would negatively affect the product's efficacy. As a result the QA department declared the product unfit for resale.

Impact:

The manufacturer suffered a complete write-off of the value of the product. It lost €2 million in immediate sales and put at risk a potential €100 million in future orders.

Clearly, the stakes are high in this new generation of pharmaceutical products. And, as healthcare providers and payers increasingly base purchasing and reimbursement decisions on a drug's therapeutic performance, it becomes even more critical to protect product efficacy throughout the supply chain.

These realities are causing manufacturers to re-think their temperature-controlled supply chains. Leading companies, and their logistics service providers, understand that the traditional cold chain is outdated. The time has come for a smarter life sciences supply chain – one that incorporates specialist-level knowledge, robust standard operating procedures (SOPs), regulatory compliance expertise, end-to-end control, global experience and dedicated IT systems to deliver cost-effective, compliant solutions.

Manufacturers can't go it alone in developing and managing this highly complex, next-generation supply chain. Pharmaceutical companies must partner with fully integrated logistics service providers and specialized suppliers that are expert in handling their temperature-controlled products. Such high-performance partnerships are based on a foundation of collaboration at both the strategic and tactical levels – all focused toward one common goal: serving the health of the patient.

This white paper looks at the dynamics that drive today's life sciences sector and how these factors impact the supply chain. It discusses four key components of a next-generation cold chain, and highlights why and how they make a difference to the manufacturer and, ultimately, to the patient.

THE STATE OF THE INDUSTRY

Two major trends are re-shaping the face of pharma today. The first is the dramatic shift in the nature of products to biologics and specialty drugs. The second is a global escalation in regulatory compliance requirements.

THE BIOLOGICS BOOM

While the growth in drug spending worldwide is healthy in aggregate, the rise in spending on biologics and specialty drugs is far more dramatic. In the United States, for example, expenditures for these new specialty drugs are expected to quadruple between now and 2020 (Figure 1). This same trend is playing out across the world, as the transition toward more structurally complex and temperature-sensitive drugs gathers momentum.

The industry's migration to these new medicines injects tremendous complexity into the distribution process:

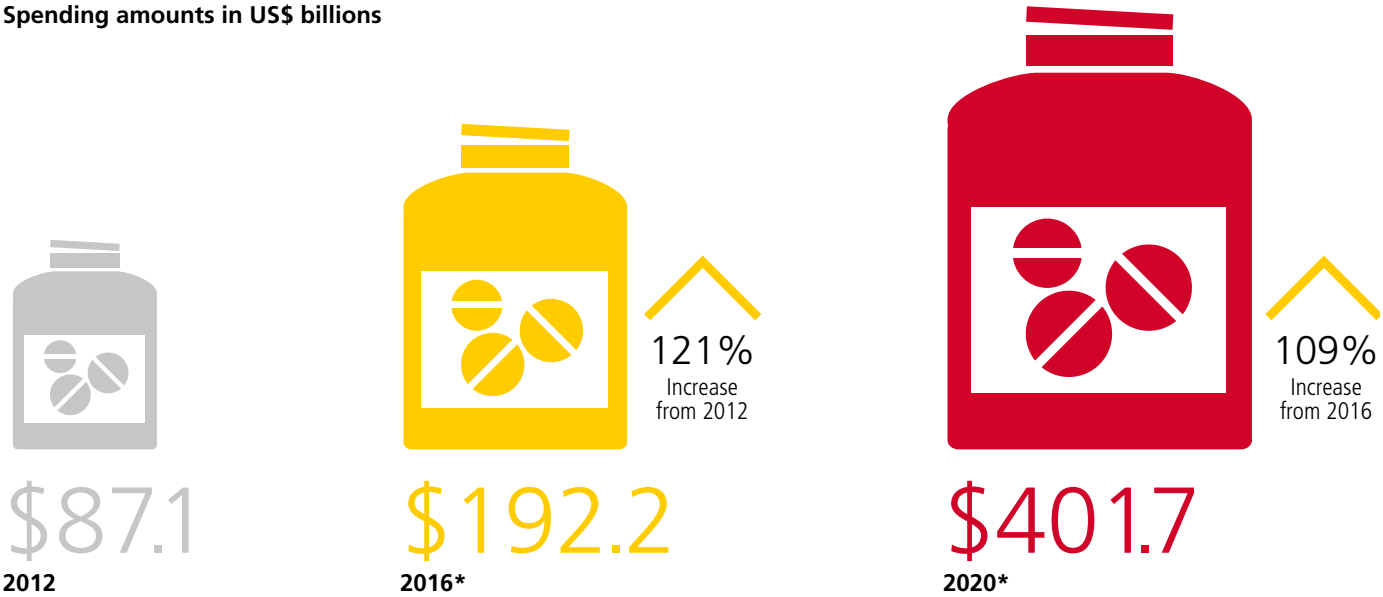
- Product must be handled within very specific condition tolerances – i.e., cold chain, frozen and controlled room temperature (CRT) (Figure 2). Failure to maintain appropriate conditions at any point in the supply chain can impact the efficacy of the drug, result in the loss of a shipment and put patients at risk.

- Biotechnology medicines often are extremely high value with annual per-patient treatment costs can exceed $100,000. This means that a single consignment may be worth upwards of $50 million.

- Because drugs often are manufactured in specialized locations, these temperature-controlled products frequently traverse the world on their way to market. They move through a sometimes-extreme range of climactic zones while en route, and travel via multiple modes with numerous hand-offs.

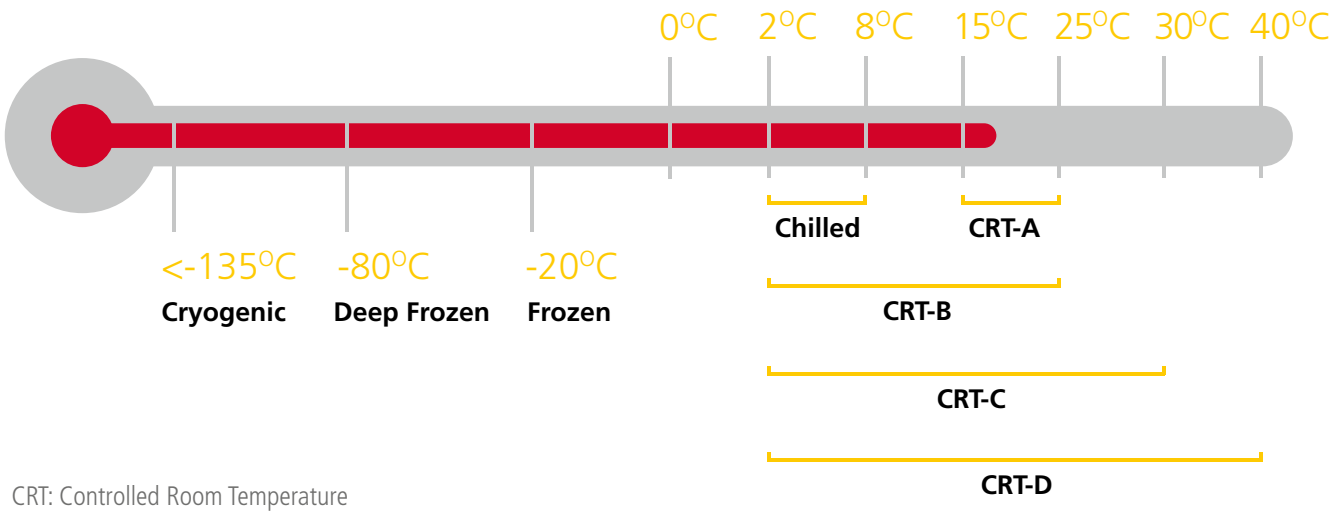
FIGURE 1: PROJECTED SPECIALTY DRUG SPENDING 2012 TO 2020

Spending amounts in US$ billions



Source: PwC Health Research Institute, Medical cost trend: Behind the numbers 2015, June 2014, analysis based on data from CVS Caremark.

FIGURE 2: COMMON PRODUCT TEMPERATURE RANGES WITHIN A CONTROLLED SUPPLY CHAIN



CRT: Controlled Room Temperature

The complexity of this business does not stop there. Many manufacturers ship product globally, and are rapidly expanding into emerging markets. Global distribution increases the number of product hand-offs, which in turn increases risk. Additionally, in emerging markets, there frequently are infrastructure issues – a lack of proper temperature-controlled facilities, transport options and handling capabilities, as well as higher ambient and container temperatures. It is not unusual for actual internal/product temperatures to be 20 or 30°C warmer in vehicles or reefers exposed to the sun for long periods.

"All of this means that product protection – preventing damage and/or spoilage – is very high on the pharmaceutical company agenda," reports Jonathan Blamey, Vice President, Global Solution Design, DHL Life Sciences & Healthcare. "In a survey of our life sciences customers, 40 percent indicated that the ability to maintain an effective temperature-controlled chain for their products is a major issue."

Not surprisingly, expenditures for cold-chain logistics are climbing. The total size of the healthcare cold chain logistic services market is expected to expand from its current figures of US$ 8.5 billion to nearly US$ 13.4 billion by 2020, according to IMARC Group's Global Healthcare Cold Chain Logistics Market Report & Forecast (2016-2020).

"In a survey of our life sciences customers, 40 percent indicated that the ability to maintain an effective temperature-controlled chain for their products is a major issue."

THE COMPLIANCE SQUEEZE

As the nature of pharmaceutical products is changing, so too are the global regulatory regimes that control them. Specifically, regulatory compliance requirements and enforcement are getting stricter. Pressure is increasing to ensure "ship-to-label" regulations are met; authorities require proof that products have not only been stored at the temperature stated on the label, but also kept within an approved temperature range during transportation.

This stepped-up regulation is largely the result of revised guidelines issued by the European Commission in 2013, which established good distribution practices (GDP) requirements for pharmaceutical products. In addition to extending enforcement to include transportation as well as storage, the European Union (EU) GDP rules expanded regulatory oversight to medicines not previously covered by temperature-control regulations – i.e., controlled room temperature (CRT) products.

As the World Health Organization explains, the focus of the EU GDP rules is on ensuring "that no weak links exist in the supply chain, [which is] critical in protecting patients from unsafe medical products."[2]

The GDP regulations do not specify exact procedures. Instead, they focus on a risk-based approach to managing condition outcomes in adherence to label requirements. This makes compliance a challenge.

"There's a lot of interpretation about what to do and how the enforcement will affect us," says one European pharmaceutical manufacturer. "Authorities are not telling you anything until they do an actual inspection. You have to figure the answers out."

Despite this interpretive uncertainty, the EU GDP rules are fast becoming the de facto standard around the world, with countries and regulatory bodies adopting variations of the requirements. For example, the PIC[3] consortia – which includes regulatory bodies from more than 50 countries, has adopted EU GDP.

Expansion of compliance requirements, particularly to CRT products, is straining supply chain operations as well as budgets. "Right now everyone's costs are going up," reports Charles Bennett, Director Global Specialty & Cold Chain Logistics at Pfizer Inc. This fuels the urgency of developing a more effective temperature-controlled life sciences supply chain.

[2]http://www.euro.who.int/en/health-topics/Health-systems/medicines/news/news/2015/02/first-technical-workshop-on-the-good-distribution-practices-gdp-of-medical-products-in-the-who-european-region, accessed 5/15/2015.

[3]Editor's Note: The Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (jointly referred to as PIC/S) are two international instruments between countries and pharmaceutical inspection authorities, which provide together an active and constructive co-operation in the field of GMP. PIC/S' mission is "to lead the international development, implementation and maintenance of harmonised Good Manufacturing Practice (GMP) standards and quality systems of inspectorates in the field of medicinal products." http://www.picscheme.org/, accessed 4/19/15.

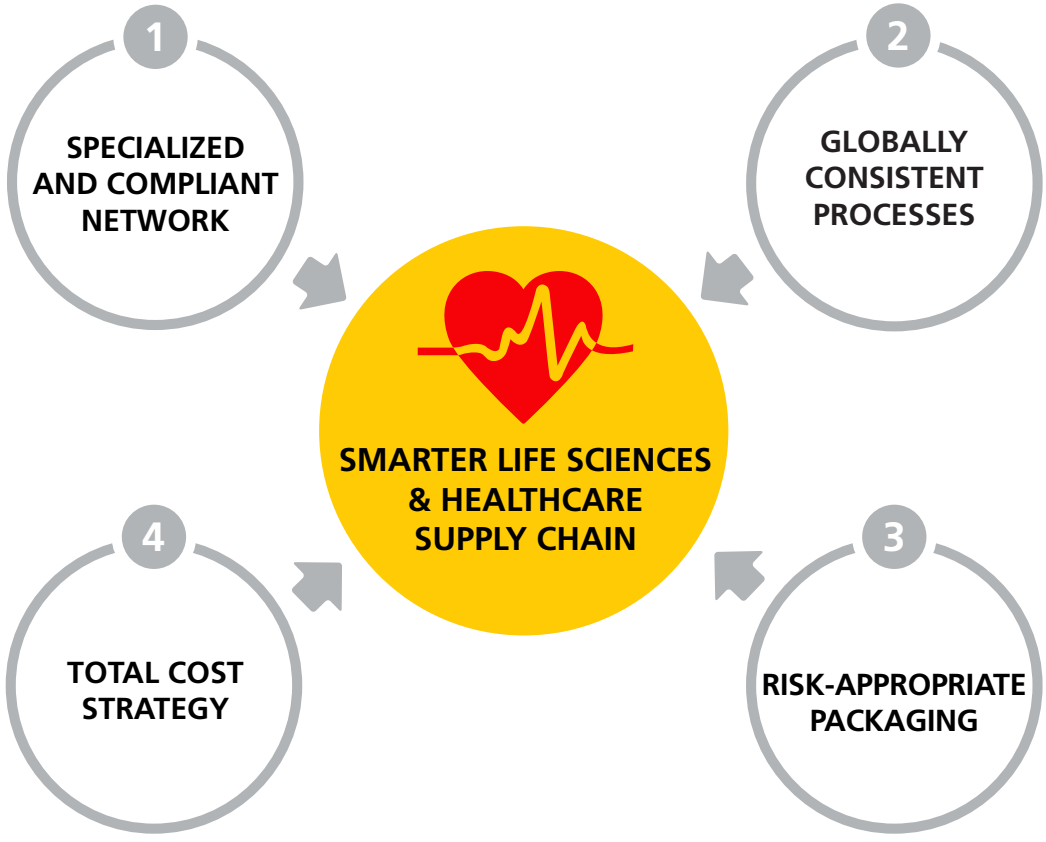
FOUR ESSENTIALS OF A SMARTER COLD CHAIN

Next-generation temperature-controlled supply chains must be consistent and robust. They must incorporate ways of mitigating risk and loss, have strong contingency capability and deliver proactive problem-resolution processes. And they must be segmented based on tiered product value, handling needs, customer service requirements and compliance rules.

Beyond this, emerging best-in-class life sciences cold chains are built on four key essentials (Figure3).

This section of the paper discusses each of these essentials and their contribution to an effective and efficient temperature-controlled supply chain.

FIGURE 3: FOUR ESSENTIALS OF A SMARTER COLD CHAIN



FOUR ESSENTIALS OF A SMARTER COLD CHAIN

1. SPECIALIZED AND COMPLIANT NETWORK

The unique requirements of cold chain pharmaceuticals demand a highly specialized and compliant network tuned to moving product efficiently, while protecting its integrity. This network consists of the facilities and assets required to handle temperature-controlled pharmaceuticals, as well as the IT systems needed to monitor and manage the global product flows. "In our physical network, we have Certified Life Sciences Stations close to major airports that operate to our GDP standards and act as an extension to our customer's own compliant network," notes Michael Terhoeven, Vice President Strategy and Development, DHL Life Sciences & Healthcare. "These Certified Stations ensure that the customer's temperature-sensitive products are held, handled and forwarded under the controlled conditions set out in the SOPs. At destination, the station receives the goods, and the process of managing and monitoring against the agreed-upon SOP continues to the point of delivery."

The physical network also may be used to position product before it enters the wholesale channel. In this case, the warehouse must be GDP certified, and may need to have a pharmacist on site or close to site to control quality. These facilities store product longer than the near-airport cross-docks, and in addition to providing standard warehousing, storage and dispatch, provide value-added services such as repacking, country-specific serialization labeling, product release, order to cash cycle management, life sciences-qualified transportation, end-to-end track and trace, and full compliance documentation.

Continued...

The key point with such physical infrastructure is that it is designed and operated for life sciences products only.

An intelligent IT platform, provided by the logistics service provider, underpins the physical network. Monitoring solutions establish checkpoints of visibility that enable more proactive control of the shipment, and allow for intervention should an adverse situation arise. Because the IT platform houses the manufacturer's SOPs, these interventions conform to regulatory and company requirements.

On a strategic level, intelligent IT networks harness the power of big data and analytics to reduce risk and make better decisions about managing the temperature-controlled supply chain. As David Bang, Global Head, DHL Temperature Management Solutions explains, "Because we have collected, aggregated and analyzed data from multiple customers, thousands of shipments, hundreds of trade lanes, and numerous types of packaging, we can identify risk trends and design the supply chain process to prevent, avoid or mitigate those risks."

Big data analytics can also help manufacturers in other ways – for example, accelerating the packaging qualification process. For a new product launch, engineers frequently spend six to 12 months testing and qualifying packaging on a one-off basis.

A global 3PL partner, on the other hand, handles thousands of temperature-sensitive shipments, so collects packaging performance data across a broad range of customers, products, package types, routes, transport

modes and temperature situations. "By looking at this aggregated performance data and identifying patterns," explains Bang, "we can advise the manufacturer about how different types of packaging perform across similar products and situations." Mining this real-life performance data can help manufacturers shorten the qualification process and support a reduction in both packaging and transportation costs.

Assets and IT provide the physical network to manage goods, but the people, and their expert knowledge in handling pharmaceutical products, make the network work. "First and foremost," says Bennett of Pfizer, "we expect people to understand that what they are handling is not just a carton of nuts and bolts. There may be a life depending on it."

Selecting a logistics partner with expert knowledge in handling pharmaceuticals is critical. "We look for a 3PL that has an entire division focused on the life sciences business," Bennett explains. "We want their whole organization to be trained in handling our types of shipment. That means they understand the unique needs of the product, they understand our SOPs, and they have a pharmaceutical mentality."

From the 3PL's perspective, this means training is a top priority, especially given the complexity and constant change in regulations and product portfolios. "We have trained over 3,000 DHL employees on GDP as part of our ongoing program," reports Nigel Wing, Vice President, Global Head, DHL Life Sciences & Healthcare. "It's not enough for us to have a best-in-class cold chain infrastructure; we must constantly invest in the people that work within it."

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2. GLOBALLY CONSISTENT PROCESSES

Effective temperature-controlled supply chains rely on well-defined SOPs to make them work. The foundation for these SOPs is comprehensive supply chain risk assessment.

"You need to understand your risks before you put product into the supply chain," explains Perry McDonald, Warehouse and Export Manager – Australia, Hospira Inc. "So you conduct risk assessments collaboratively with your partners, and build policies and procedures around those risk findings. " These include mitigating actions – like what happens to my product if the aircraft is delayed or breaks down; what happens if a forklift puts a tine through the side of an air cargo container of cytotoxic injectables and it starts leaking? They also include learnings from incidents."

McDonald asks his 3PLs to develop their own risk assessment of his products and lanes. He and the 3PL then blend that assessment with Hospira's procedures to arrive at mutually agreed-upon SOPs. "This collaborative approach is very important, especially if you're making a change in your supply chain," McDonald says. "The greater the risk in the supply chain, the tighter the collaboration on SOPs between the manufacturer and the forwarder needs to be."

Pfizer has two levels of temperature-controlled SOPs: internal site procedures and external logistics partner SOPs mapped out by lane. "Our lane SOPs reside with our forwarder and we have access to them," Bennett reports. "These are the work instructions on how to move a temperature-sensitive product from point A to point B. These SOPs reflect the needs at the point of origin as well as those at the destination."

SOPs address the product characteristics, season, weather conditions, in-transit and in-storage condition requirements, documentation needs, in-transit monitoring and compliance. They are a constant work in progress. "We are always fine-tuning on our SOPs to optimize and improve the way we are handling our flows," reports Aurelian Sarazin, Distribution Manager - EMEA APAC, Bristol-Myers Squibb Co. (BMS). "This is very difficult to manage because our SOPs change."

In particular, BMS is concentrating on standardizing and aligning its SOPs across all of its trade lanes, markets and destinations. The goal is to reduce complexity while still ensuring product safety.

"We then have to make sure our supply chain partners implement those standards and solutions globally," Sarazin continues. "This is difficult because frequently, there are big differences between logistics providers and how they operate. Even within a single partner, a solution may be available in some areas and not in others, and their execution may be inconsistent across regions. Good communication is essential."

The goal is to reduce complexity while still ensuring product safety.

3. RISK-APPROPRIATE PACKAGING

The third essential of a smarter temperature-controlled supply chain is packaging. In principal, shippers of temperature-controlled pharmaceuticals have a broad choice of options. Essentially, there are two basic categories of packaging: active and passive.

Active systems range from discrete packages and full containers/trailers to entire aircraft. They use an energy source combined with thermostatic control to maintain temperature. Passive packaging solutions look like conventional packages but use materials such as water/ice or dry ice to keep products at the desired temperature. Unlike active solutions, passive packaging does not respond actively to adverse temperature conditions.

The choice of packaging is a matter of balancing the cost with the risks and benefits of a particular option. Manufacturers must consider the value of the pharmaceutical product, its temperature-management needs, regulatory compliance requirements, customer and market risk, and total cost in making their selection. "The analysis is based on a single question," observes Joachim Kuhn, CEO of thermal packaging company va-Q-tec. "How much risk are you willing to assume?"

Technology has become an increasingly important component of packaging solutions, particularly with active systems. Active packaging solutions will soon incorporate report-back technology such as GPS and telemetry to ensure the safety of shipments. For example, Envirotainer's temperature-controlled container "will be able to communicate with us throughout the cold chain, telling us its position, temperature, battery level, whether it's open, whether there's risk of theft or damage from shocks,"

notes Mattias Almgren, Deputy CEO of Envirotainer. "It will report a number of crucial data points that help us ensure the container is doing its job and the process is going the right way."

Such report-back capabilities allow proactive intervention to ensure product integrity, thereby reducing overall risk.

While packaging – even the most expensive active solutions – protects the product, it isn't the complete answer. "You can have the most robust packaging material but it's no good if the handling is poor," stresses Wing of DHL. "It takes people to make the cold chain work, so it comes back to having good SOPs, knowledge about the product and training."

4.TOTAL COST STRATEGY

Smarter cost management is the fourth essential of the next-generation life sciences cold chain. Leading manufacturers and their logistics partners are evolving away from simply managing costs on a purchase-price basis, to a total cost of ownership (TCO) model.

Strictly defined, TCO is the compilation of direct and indirect costs associated with a purchase, transaction or activity. In the case of the temperature-controlled pharmaceuticals supply chain, TCO carries a much broader definition to include everything from patient safety, product and market share losses, to brand risk.

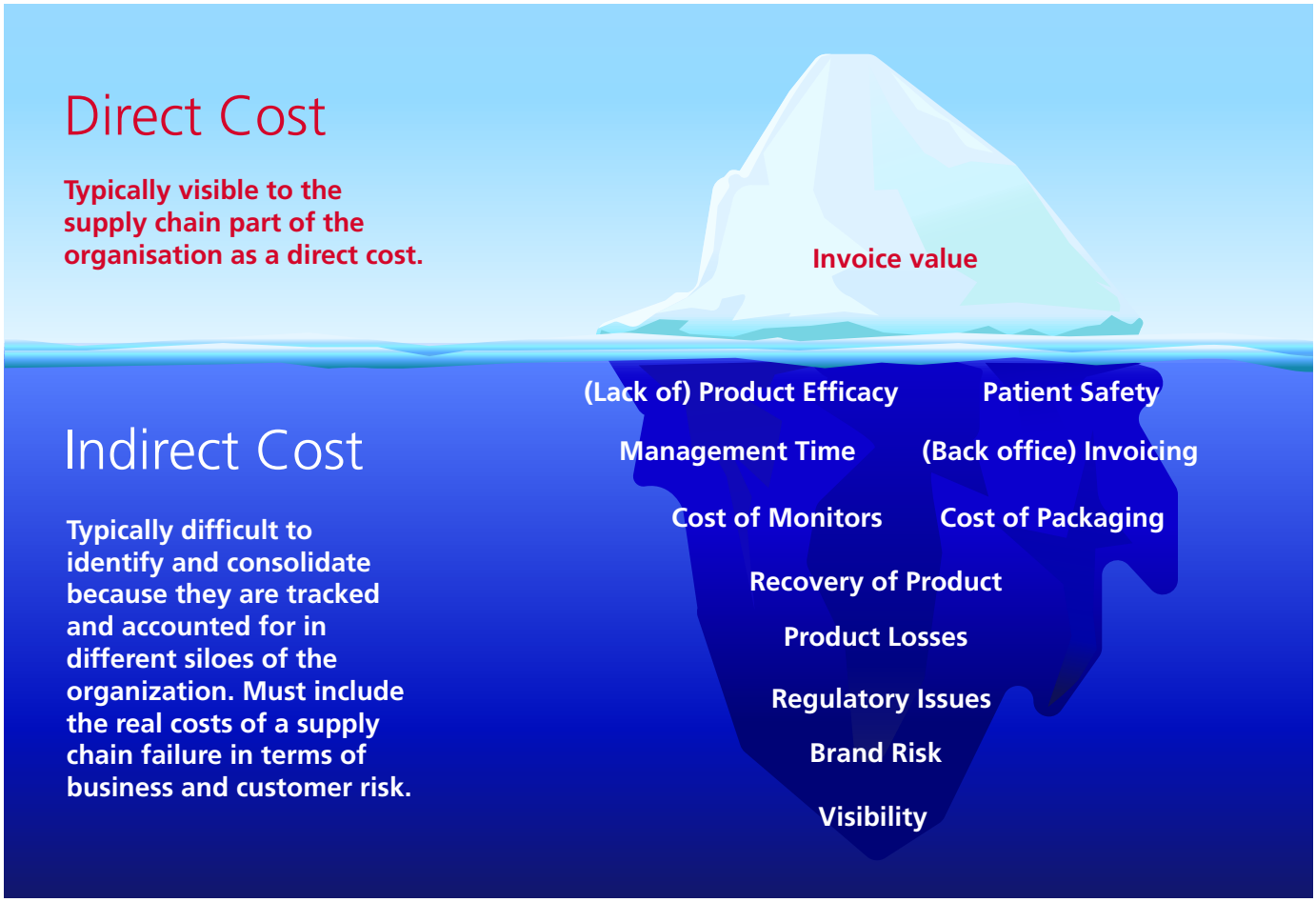
"It is easiest to think of TCO as an iceberg, with the direct cost – such as the invoice value of a service – representing only a fraction of the whole cost picture," explains Blamey of DHL (Figure 4). "The hidden costs carry the real risk to the business."

Identifying and calculating these 'hidden' costs, and factoring them into a business decision or operating plan is not easy. "Within large pharma organizations, costs often are spread across various departments, further hindering a strategic approach to cost management," observes Angelos Orfanos, President, DHL Life Sciences & Healthcare. "If a product is damaged or lost then that's one cost line, the cost of packaging is in a different line, transportation is in a different line, and so on. It is often difficult to get a total cost picture because these costs are tracked separately."

"We definitely are challenged to manage end-to-end costs," acknowledges Sarazin of BMS. "We try to build a total cost for a packaging solution, for example. We look at the cost of the box, the additional transportation cost it generates, the packaging waste management or return cost, the handling and storage, and so on. And we look at these on a global basis, which gets very complex."

Continued...

FIGURE 4: ELEMENTS OF A TOTAL COST APPROACH



Source: DHL, 2015

Economizing on one aspect of the temperature-controlled supply chain without factoring in the total cost can and often does backfire. Valgeir Petursson, Executive Director of International Logistics at Actavis plc, offers an example. "If a logistics manager sends a shipment of five pallets on a dedicated truck, let's say that costs €4,000. If he puts that same product on a consolidated shipment, the freight rate is far lower - €500 to €1,000. The manager is very happy with his savings - until the consolidated load is ruined by a temperature excursion caused by extreme spikes or dips in temperature during the co-loading. He has now lost €200,000 worth of product by trying to save €3,000."

The tangible loss is almost nominal when compared to the total cost of the loss. "Companies have to pay penalties to their customers for not delivering as promised," Petursson continues. "And in some markets, if you're not able to provide product, someone else will, so you lose that sales opportunity. More importantly, though, once customers start using another product, many won't change, so you've lost that market share permanently. That can translate into millions."

Technology assists in making smarter, cost- and performance-optimized decisions, as Novartis AG has learned. "Our focus on cost has always been quite strong, but it wasn't based on complete performance data," explains Ladislav Vondrášek, Senior Process Expert/Vendor Manager at Novartis. "It wasn't until we started doing full temperature monitoring in our supply chain that we discovered we could do better at reducing excursions."

Now, armed with more data, Novartis can judge where to spend more money to achieve the right level of protection. "This is not a risk-based approach; it's a performance-/data-based approach that delivers greater reward," Vondrášek observes. "The additional cost of applying this technology is more than offset by better performance."

Pharmaceutical manufacturers are in the early stages of adopting an insight-driven TCO approach. Pursuing this strategy has the potential to save millions in total supply chain costs, while fueling sales and market share growth.

PARTNERING FOR SUCCESS

Taken together, the four essentials of the smarter life sciences supply chain drive powerful benefits. They safeguard product, effectively manage complexity and risk, reduce total cost and improve profitability and competitiveness. In the scenario cited at the beginning of this paper, application of these four essentials would have handled the product appropriately, prevented the temperature excursions, provided the right packaging and transport solution, protected the product, eliminated the temperature excursion risk, and completely avoided the millions of euros in actual and potential lost sales.

Beyond executing the specifics of infrastructure, data analytics, people, packaging and total cost management, the success of a temperature-controlled pharmaceutical supply chain comes down to one powerful concept: collaboration. "You absolutely have to have a good partner," McDonald of Hospira stresses. "My choice in a freight forwarder is critical. Pharma is a niche business and I need logistics providers that understand my business. I am looking for a long-term relationship with a trusted partner." This relationship starts with assessing the risks and designing the solution, and goes all the way toward executing final delivery – safely and securely.

"Our most successful supply chain outcomes come from when we have good collaboration along the whole chain," agrees Almgren of Envirotainer. "The more we are able to break down the walls between shippers, airlines, freight forwarders, packaging suppliers–the more we all succeed."

At the end of the day, the main goal of every pharmaceutical company is to serve patients in maintaining and/or regaining their health. Products adulterated because of insufficient conditions in the supply chain thwart this goal. "Even though we are in business to make a profit, we have a responsibility to society to eliminate disease," Bennett of Pfizer concludes. "It's in our DNA."

ABOUT THE AUTHOR

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