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# Value of the Cold Chain:
## Relevance of Cold Chain in Site Selection for the Life Sciences Industry

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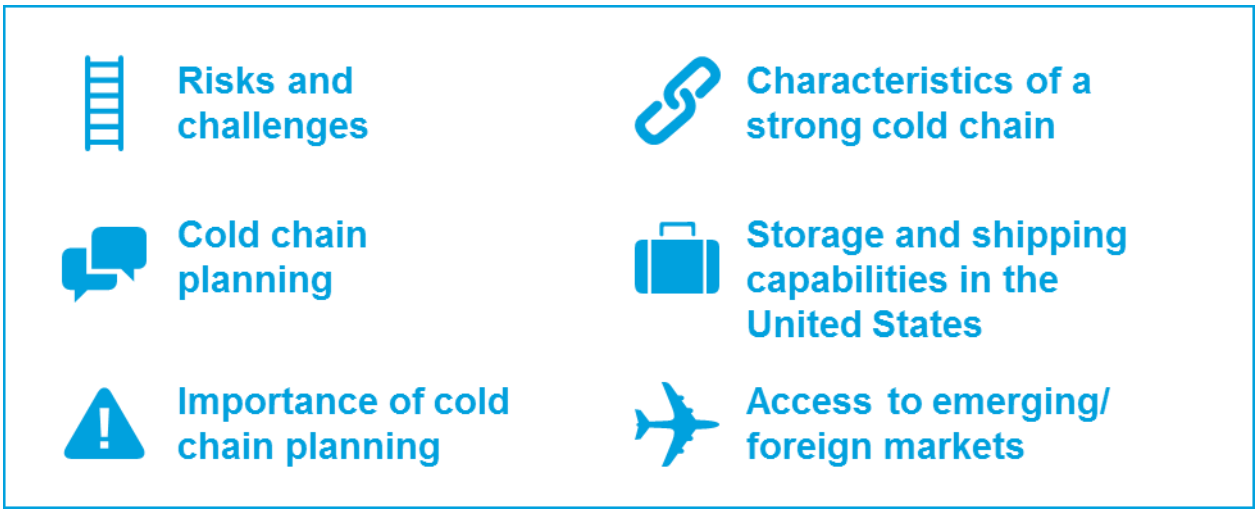
# Introduction

Temperature-controlled supply chain, often called cold chain, refers to the transportation of products along a supply chain that must be maintained within a certain temperature range in order to uphold the integrity of the products and is most commonly used by chemical, food, and pharmaceutical industries. Within the pharmaceutical industry, the emergence of bioscience has significantly increased the demand for cold chain infrastructure, as biologics, blood products, and vaccines all require a stringent set of guidelines that must be followed in order to ensure product safety and viability. Variations in temperature can partially or wholly void a shipment and lead to millions of dollars in lost sales for the company. As well it is common for companies to add multiple linkages to a global supply chain with little thought to the complexity and risk associated with extending the cold chain. Many companies realize flaws in their cold only after it has reached a level of complexity that is difficult to simplify.

This executive briefing examines what companies should consider to ensure safety and integrity of their products, including risks and challenges, importance of planning, and characteristics of a strong cold chain. We also look at factors that enable greater reach of the products by looking at the storage and shipping capabilities in the United States and access to emerging/foreign markets through enhanced connectivity.



# Risks and challenges

Companies with products in the cold supply chain face four major risks and challenges:

- **Product adulteration** — poses the biggest risk as it can wholly or partially void an entire shipment
- **Regulatory compliance** — risks due to lack of education on regulations around temperature-sensitive pharmaceutical products
- **Access to markets** — restrictions due to incomplete cold chains
- **Cost containment** — due to lack of attention given to minimize cold chain costs

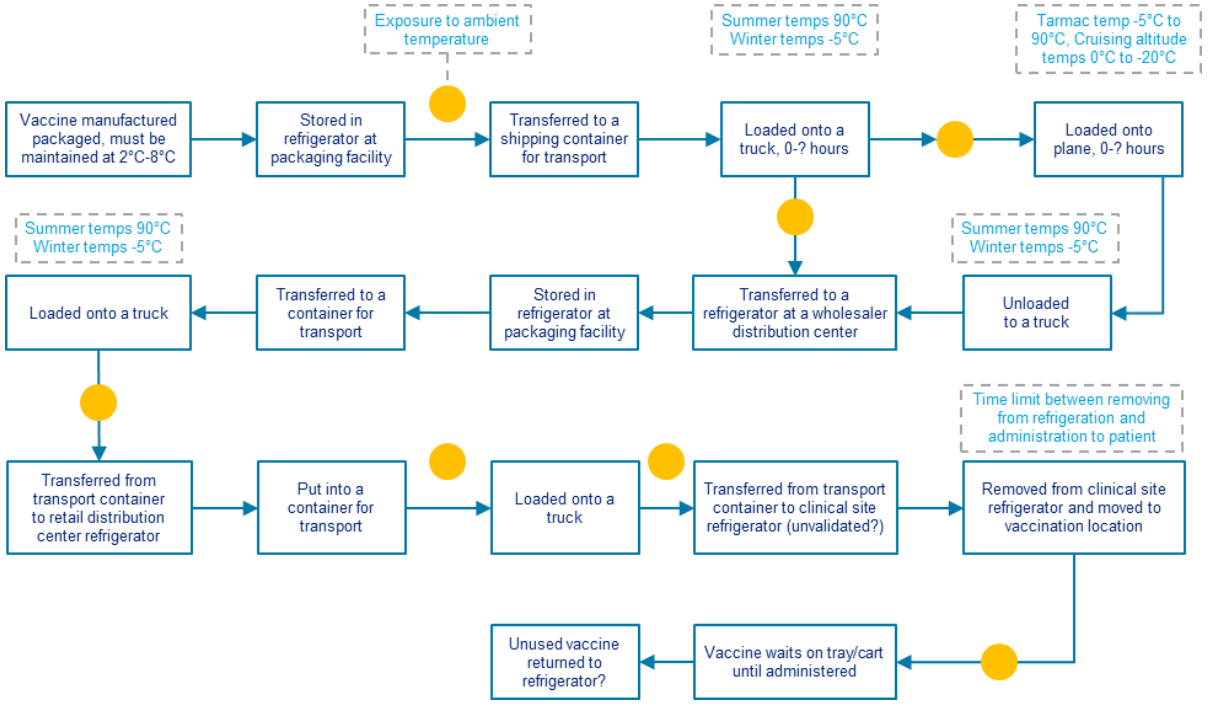
## Product adulteration

For research and development (R&D) and manufacturing alike, transporting some drugs is risky because any variation from a specified temperature range can wholly or partially void a shipment, and the risk of this occurring exists along the entire supply chain. The process map below provides a good example of potential points of exposure along a given supply chain. Importantly, these high-risk points can be difficult to monitor, so it is imperative for companies to invest in a secure cold chain.

**Sample causes of product adulteration**

- Weather delays
- Interrupted power supply
- Availability of en route storage
- Delays in pick ups
- Overexposure to unregulated climate during handling
- Inadequate packaging
- Truck availability

**Points of exposure along a cold chain**[1]




## Regulatory compliance

In most cold chains, regulatory compliance is threatened by an overall lack of education on regulations and guidelines around temperature-sensitive pharmaceutical quality assurance. This requires companies to invest in training employees, to thoroughly vet stakeholders, and to set up appropriate testing and documentation procedures along the many links of a given supply chain.

For international transportation, the complexity of training and monitoring employees along the cold chain is further complicated by varying international and multinational regulators. Fortunately, as the biologics industry continues to globalize, countries are increasingly looking to requirements by the Federal Drug Administration (FDA) as well as the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). Though the ICH's rules are not legally binding, they are quickly becoming the standard for international shipment.

## Access to markets

Incomplete cold chains often restrict the market size, and thus revenue potential, of commercial drugs. In these cases, inadequate infrastructure and vehicle availability are the most significant barriers to overcome.

In developed markets, companies are challenged to find cold storage space in the distribution process and commonly lack cost-effective access to major hubs (i.e., airports, seaports, large storage facilities) with the capabilities and expertise needed to handle, store, and prep for short- and long-distance (international) cold chain transportation. Hubs with limited capabilities and some experience in cold chain processes can be just as risky as those without any, because even the smallest variance from temperature ranges and other environmental controls can void part or all of shipment.

[1] Fisher Bioservices 2013 report: Cold Chain Qualification: 5 Questions You Must Ask When Shipping Biologics.

Gaining access to developing markets can be incredibly difficult. In many of these markets, product must be shipped internationally, and as the length of the trip increases, so does the risk of protective packaging failure and harmful temperature exposure. Even in developing markets where product is manufactured, limited and unreliable road infrastructure limit total potential market access.

Like poor road infrastructure, vehicle availability can reduce the size of an accessible market. It can also cause random disruptions in the cold supply chain, as weather conditions, natural disasters, accidents, and mechanical failure are largely unpredictable. For this reason, it is advantageous to locate distribution nodes throughout regions that have infrastructure to support excess product storage and have flexible vehicle fleets to meet unexpected demand.

**Avoiding unnecessary delays**

When exporting or importing products, inexperienced or inefficient customs offices can delay approval processes that place the shipment at unnecessary risk. Proactive companies maintain reliable supply chains by seeking out locations with cold chain experience and infrastructure.

## Cost containment

It is not unusual for site selection decision makers to evaluate supply chain optimization alongside other critical needs. As a percentage of sales revenue for a given product, supply chain expenditures are usually much smaller relative to labor or materials expenditures. For this reason companies tend to first invest in the mitigation of other risks versus challenges to product movement. However, this can lead to redundant processes, avoidable links that elongate the supply chain and overpriced services. Optimizing the supply chain should be prioritized if resources are available, as it can achieve cost and time savings, particularly through inventory carry as well as product loss, and mitigate potentially significant risks.

With each addition of a supply chain link, inventory carry stock must be increased, and opportunities for failure are introduced. It is not unusual for bio-pharmaceutical companies to move their products across multiple continents and back again as products move from bulk production, to fill/ finish, to packaging and then ultimately market distribution channels. Each product movement should generally require multiple weeks of reserve inventory. That added inventory carry reduces the market available supply and delays revenue recognition. More importantly, each product movement adds increased risk for a failure in the supply chain leading to loss of product and potentially delays which impact ability to get to market. Most executives in the bio-pharma industry have likely dealt with this issue at one time or another in their career. Most organizations fail to give proactive advanced consideration to the supply chain impacts, often addressing the issues symptomatically when problems arise. With the ever increasing demand for cold chain resources across a range of industries, long term supply chain planning is necessary to avoid issues which arise only after the supply chain has grown too complex to easily simplify.

### Cold chain supply and demand

Between 2006 and 2012, biologics sales doubled to reach $124 billion[2] and grew from 14% of over-the-counter pharmaceutical sales to 21%[3]. Such growth will continue to raise demand for cold chain infrastructure over the near to medium term. This could potentially cause a supply squeeze for cold chain-related resources, as investments in additional infrastructure may fail to meet industry demand. This scenario would have two significant impacts on companies that utilize cold supply chains. First, it could raise the short-term costs of product transportation, storage, and distribution as companies along the supply chain react to excess demand. Second, it could virtually block access to certain markets where resources are likely to remain limited (e.g., emerging markets).

Given this potential risk, companies should invest in understanding the capacity limits of their current supply chains and identify locations that can provide secure market access in the case of a cold chain supply squeeze. Such locations will have already made significant investments in the infrastructure and resources needed to move a large amount of product.

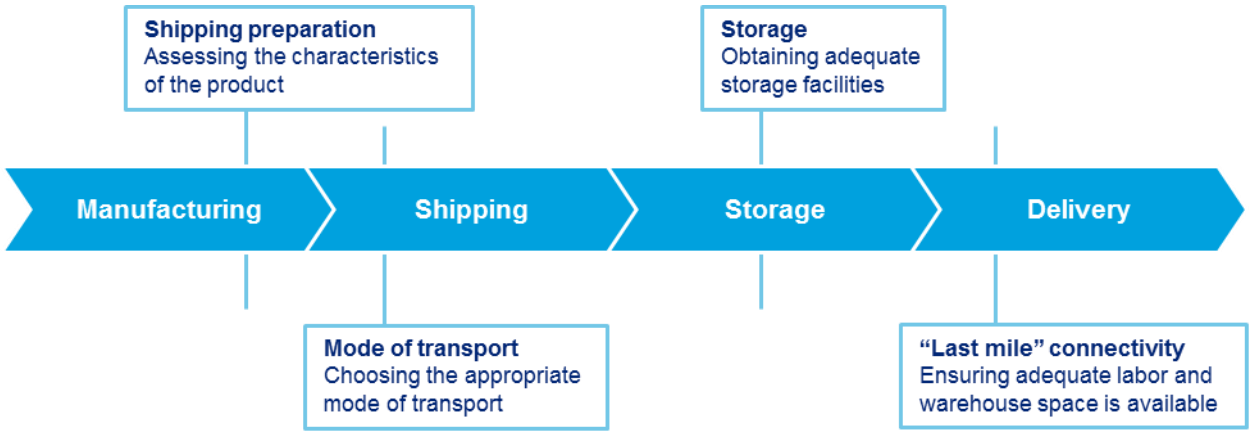
[2] Press article “Blockbuster Biologics 2012: sales are double that of 2006 driven by strong growth of recombinant antibodies” published by Le Merie in May 2013.

[3] World Preview 2016 published by EvaluatePharma in May 2010.

# Cold chain planning

Many businesses fall short of securing the proper cold chain for their business needs. Although this is partially due to the complexity of the supply chain, failures can more often than not be traced back to a general lack of planning.

A planning exercise for cold chain should consider the following components:




Among the various components, advance planning for securing adequate storage facilities is important as it involves undertaking significant investment for setting up storage facilities and a long lead time to build the facility. Given the uncertainty associated with the timelines for moving pharmaceutical products, regions with ample cold storage facilities offer a distinct advantage for pharmaceutical companies.

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# Importance of cold chain planning in drug development and manufacturing

The biopharmaceutical industry perceives functions such as logistics and supply chain management as secondary objectives as they are focused on the goal of discovering treatments and cures for devastating diseases. However, competition within the drug development industry is intensifying and an optimized clinical-trial supply chain can provide a strategic advantage to accelerating drug development.

The globalization of clinical research has added more complexity to the safe, punctual, and compliant transport of study drugs and other temperature-sensitive materials. Biopharmaceutical companies are developing more large-molecule drugs, which are much less stable than most small-molecule drugs, and increasing numbers of tissue samples are being collected to support biomarker research. These industry trends require a fully developed cold chain to ensure samples are not damaged in transportation.

Any weak link in the chain can compromise drug or sample integrity, breach security, delay shipments, and ultimately lead to financial loss or liability. Moreover, there are significant repercussions associated with clinical-trial samples being lost in transit or rendered useless because of temperature variation during transport. That could have a trickle-down effect that may delay studies, thereby increasing the time to drug approval and reducing the potential time a drug is on the market. A delay to market could cost a sponsor millions of dollars in potential sales. So it is vital for clinical-trial materials to be packaged and shipped in compliance with industry and government standards and to be closely monitored by properly trained individuals.

**Industry view**

"From the onset of manufacturing, the very first manufacturing piece through to the end product for the clinical trial, there needs to be a process for managing transportation from the beginning. It all gets down to product management at the end of the day and if a firm can specify what Active Pharmaceutical Ingredient, what dosage form, what package style, they can also specify from the onset the transportation program and build that into the whole clinical trial program so that when the product starts to move around the country and other countries the program is known. It can be very cost-efficient because you get time to study."

*— Mary Foster, Chair of U.S. Pharmacopeial Convention Committee on Storage, Packing and Distribution*

# Characteristics of a strong cold chain

A strong cold chain should account for several factors during the movement of products from the manufacturing facility to the end consumer. The following aspects should be considered when developing a strong cold chain:

- **Shipment preparation:** Assessing the characteristics of a temperature-sensitive product is vital before it is moved. The product being moved should be at its desired temperature. Cold chain devices are commonly designed to keep a temperature constant, but not to bring a shipment to this temperature, so they would be unable to perform adequately if a shipment is not prepared and conditioned. A strong cold chain should ensure that the shipment is prepared and conditioned appropriately and that the temperature of the shipment is maintained at the prescribed level.
- **Choosing the mode of transport:** Several key factors play into how the shipment will be moved. Distance between the origin and the final destination, the size and weight of the shipment, the required exterior temperature environment and any time restrictions (perishability) of the product all affect the choice of transportation options. The cost/perishability ratio becomes a factor in modal choice.
  - **Air:** Air is the most frequently used mode of transport by the pharmaceutical industry for drugs that are sensitive to temperature variations and require a temperature controlled environment.
  - **Road:** A good network of highways and availability of temperature-controlled trucks are important as they provide last-mile connectivity.
  - **Sea:** Although ships are not the preferred mode of transport for temperature-sensitive pharmaceutical products, quality cold chain warehousing infrastructure at seaports provides pharmaceutical companies a cost-effective alternative for transportation of drugs.

**Atlanta's air connectivity**

Atlanta is home to the world's busiest airport and has direct connectivity with most Latin American cities. Hartsfield-Jackson Atlanta International Airport's Perishables Complex is the only U.S. Department of Agriculture approved site in the Southeast to apply cold treatment, and has recently finished building a new 17,000-square-foot USDA plant, tripling the capacity of the existing perishables complex.

- **Custom procedures:** Custom procedures can be very important since cold chain products tend to be time sensitive and subject to more inspection than regular freight (e.g., pharmaceuticals and biological samples). The difficulty of this task differs depending on the nation and the gateway since there are variations in procedures and delays.
- **Storage:** Planning for adequate storage is a key consideration in setting up an efficient cold chain, as it requires significant investment to set up cold storage facilities. It is crucial for a company to understand how a location's storage capacities will affect the volume it can ship and the markets it can reach.
- **The "last mile":** The last stage is the actual delivery of the shipment to its destination, which in logistics is often known as the "last mile." Key considerations when arranging a final delivery concern not only the destination, but the timing of the delivery so the critical labor and warehousing space is available. Trucks and vans, the primary modes of transportation for this stage, must meet the specifications necessary to transfer the cold chain shipment.

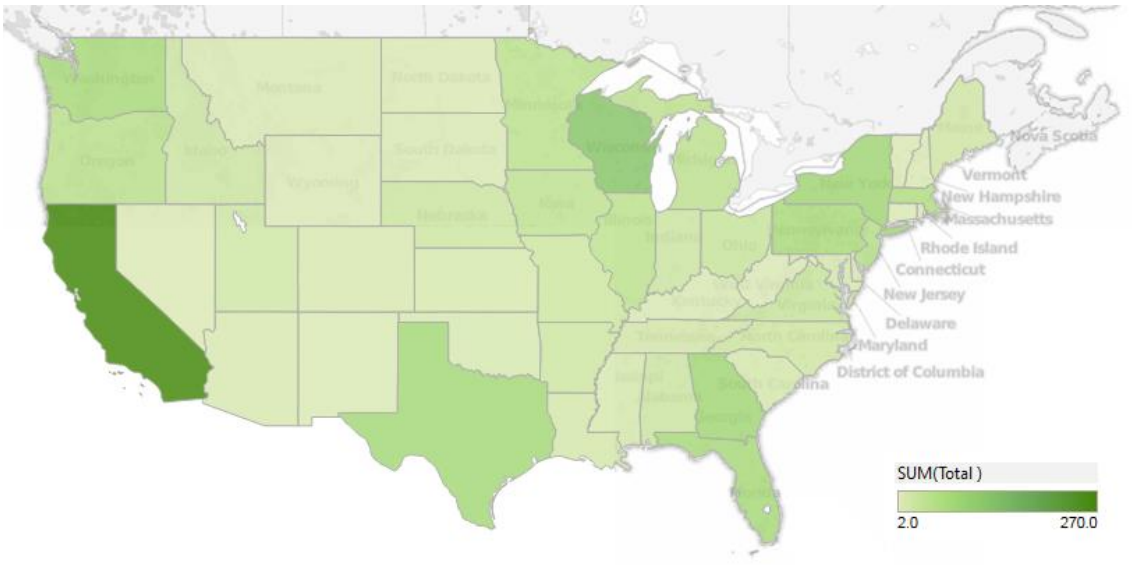
**Warehousing facilities in Georgia**

Atlanta-based Americold Logistics LLC operates the largest cold storage network in the world with a total capacity of 1.1 billion cubic feet[1], and operates many cold storage warehouses in the state. Also, UPS Healthcare Logistics[1] has made a significant investment and has more than 200,000 square feet of warehousing and distribution space in Georgia specifically for life science companies.

# Prevalence of storage and shipping capabilities in the United States

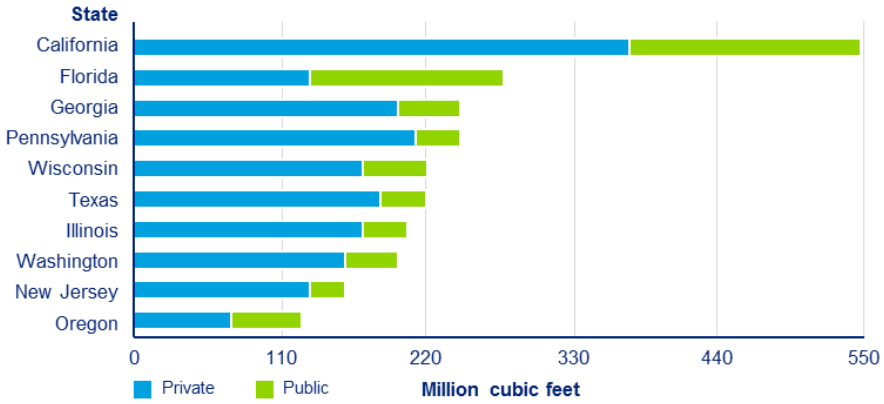
The prevalence of storage and shipping capabilities varies significantly across states. The map below shows the number of refrigerated warehouses in the United States by state.

**Number of refrigerated warehouses in the United States by state**




Georgia ranks in the top five states in the United States in terms of the number of refrigerated warehouses. However, it ranks third in terms of gross refrigerated space available as the warehouses in Georgia are generally larger than in other states.

**Top 10 U.S. states by gross refrigerated space in 2013[4]**




[4] USDA report titled “Capacity of Refrigerated Warehouses 2013 summary” published in January 2014.

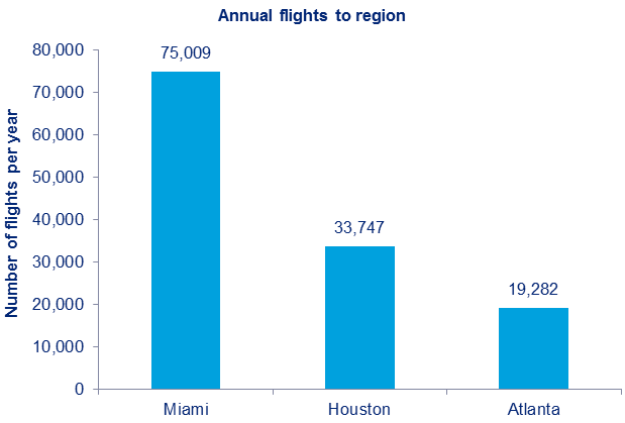
# Access to emerging/foreign markets

The emerging markets are high-growth markets that present opportunities for pharmaceutical manufacturers to expand their product reach. However, emerging markets pose many operational and regulatory challenges for manufacturers like frequent power disruptions that affect the maintenance of cold chain and lack of infrastructure (lack of quality ports, highways, and cold storage facilities).

For U.S. pharmaceutical companies, the Latin American countries present a big opportunity due to their proximity to the United States and growth potential. U.S. merchandise exports to Latin America and the Caribbean grew by 53 percent from 2009 to 2013 to reach $169 billion. Also, as per a recent survey, 50 percent of participants are planning to increase their supply chain activities in Central America within the next three years. The graph below depicts the growth in U.S. merchandise trade with Latin America and the Caribbean (LAC).


Miami, Houston, and Atlanta are the top three hubs for trade with Latin America. The graphs below depict the annual flights to the region from these three cities.[5]

[5] The Canadian trade commissioner service note on “South Florida as a gateway to Latin America and the Caribbean. 2014”


Annual flights to region
Number of flights per year
80,000
70,000
60,000
50,000
40,000
30,000
20,000
10,000
0
75,009
33,747
19,282
Miami
Houston
Atlanta

# In summary

Corporate deployment decisions are often driven by talent, market costs, and local market access. However, as companies grow the interlinkages of the cold supply chain are not always given full consideration. Growth of activities such as bulk, fill/ finish, packaging and distribution add complexity across the network. Given the potential and significant risk to both patient health and fiscal impacts, companies should consider the implications of a location's access to cold chain infrastructure. Each company's business model, global market and operations infrastructure vary. However when evaluating cold chain as a factor in site selection decisions, consider the following questions:

- How many product movements are necessary?
- Can co-location of operations such as bulk, fill/ finish, and packaging reduce number of product movements?
- Do the operations have proximate access to transportation facilities with cold chain capabilities?
- Can the location meet proximate access (road) and global access (likely air) needs with cold storage capabilities that meet your product needs?
- Is the location of the operation(s) able to readily access growth markets?
- Does the location and its place within the network allow for flexible growth?

Companies that invest adequate time to understand and answer these questions in advance can often avoid long term supply chain problems. The capital investments in operations along the biopharmaceutical supply chain are significant and it is often difficult, expensive and time consuming to unwind a complex supply chain. Therefore it only benefits companies to strategically factor in considerations for near and long term supply chain along with other relevant operation drivers such as talent, tax and costs when making site selection decisions for operations throughout their value chain.

**Value of the Cold Chain: Relevance of Cold**

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