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WHITEPAPER

# Considering the clinical supply chain in vaccine trials: Special handling required

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patheon

# Abstract

Vaccines are one of the most useful and cost-effective means of reducing illness and death from infectious diseases. With hundreds of vaccines in research and development worldwide, vaccines are among the fastest growing segments of the biopharmaceutical market today.[1] The interest in vaccines is fueled by a variety of factors. Among them: The COVID-19 pandemic, the impact of globalization, technological advances in biotechnology, post 9/11 concerns about biological warfare, the emergence and reemergence of diseases such as West Nile Virus and tuberculosis, and scientists' pursuit of new vaccine targets such as cancer and Alzheimer's disease. Another key contributor is the recognition by principal vaccine purchasers—healthcare providers and governments, whose ranks have swollen to include those of emerging markets such as China and India— of the ability of vaccines to reduce healthcare expenditures and increase quality of life through disease prevention.

The renewed investment in vaccine development has been accompanied by formidable challenges—both for biopharmaceutical research companies pursuing the next generation of products, as well as the clinical supply chain industry, to which responsibility for packaging, labeling, storing and delivering vaccines for global clinical trials has been outsourced. In addition to their cost and complexity to develop and manufacture, vaccines must be stored, transported and maintained at controlled temperatures in a "cold chain," a strict system of temperature and stock control to assure their potency and safety. Successful cold supply chain demands planning, partnering and attention to detail; a single broken link can result in loss of scarce resources and time, the twin currencies of the biopharmaceutical industry.

Thermo Fisher Scientific is a global leader in clinical trial supplies through its Patheon™ Fisher Clinical Services℠ offering. Today, half of our projects involve controlled temperature or cold chain products, a proportion that has been increasing steadily as the number of global vaccine trials escalate. This paper discusses how we are meeting the challenges of cold supply chain for global vaccine studies. Also included are planning recommendations for biopharmaceutical companies preparing to scale up to global vaccine trials.

## The importance of vaccines: Preventing and treating disease

Vaccines are one of the most effective means of reducing illness and death from infectious diseases, which were a leading cause of death in the western hemisphere in the early 20th century and remain so in much of the developing world.

Vaccines function by eliciting an immune response in the body against a pathogen, or disease-causing agent, to prevent or treat disease. Today, there are hundreds of vaccines in various stages of research and development at biopharmaceutical research companies around the world. It takes an average of 10-15 years to develop a vaccine at a cost of $1.3 billion, about $400 million more than average development costs for a drug.

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Traditional prophylactic or preventive vaccines have been used for decades to prevent diseases such as polio, measles and influenza. Additional prophylactic vaccines are in development today to prevent a host of infectious diseases, ranging from dengue fever and malaria to meningitis and HIV/AIDS.

Recently, researchers are increasingly interested in developing another type of vaccine, known as a therapeutic or treatment vaccine. These vaccines work in conjunction with the body's immune system to potentially treat patients living with diseases such as multiple sclerosis and cancer. Scientists are also working to develop therapeutic vaccines for chronic diseases, such as hepatitis B and C, herpes simplex and Epstein-Barr virus infections, as well as addictions.[1]

## Characteristics of vaccines: Why vaccines require special handling

Although vaccines are powerful weapons against disease, they are surprisingly fragile and require specialized handling throughout their life cycles in order to remain safe and efficacious. This first rule of handling vaccines is that of recognizing that there is no one-size-fits-all solution.

**Biologic-based.** Put simply, vaccines are fragile. Vaccines belong to a class of pharmaceutical products known as biologics which are produced from living organisms. A number of vaccines are, in fact, composed of live, attenuated versions of pathogens.

**Unknown stability.** In the early stages of development, the stability or shelf life of a vaccine may be unknown. For clinical supply chain managers this means the logistical stakes are high, leaving little room for error. A product could, for example, fall out of specification during the course of a clinical trial, requiring replacement. For this reason, the Thermo Fisher team conducts risk analyses to determine exactly when the vaccine is required at trial sites versus when supplies must be shipped to arrive just in time.

**All vaccines are temperature-sensitive.** Like perishable foods that require refrigeration, vaccines are highly sensitive to fluctuations in temperature. They irreversibly degrade and lose efficacy rapidly if they become too hot or too cold. As a result, they must be stored, transported and used within what is known as a "cold chain," a strict system of temperature and stock control that ensures the potency and safety of vaccines. Cold chain compliance requires careful documentation, tracking of vaccines at every level, and adherence to strict temperature requirements at all times.

The typical temperature requirements to maintain vaccine stability are +2°C to +8°C or 8°F to 46°F. Should a vaccine experience a temperature excursion, it must be discarded and replaced at significant cost.

Financial considerations aside, the supply of vaccine in early development is often limited and replacement product may be difficult or impossible to obtain within tight trial timelines.

**Impact of global trials.** The increase in the number of vaccine clinical trials migrating to cities like Shanghai, Mumbai and Moscow has been accompanied by new supply chain challenges.

In addition to huge fluctuations in temperature from country to country, lack of infrastructure in emerging markets means that storage and transport conditions are often less than ideal, making the logistics associated with cold chain compliance all the more challenging.

Desirable trial locations include Asia, where China and India are together home to 2.4 billion potential patients; Eastern Europe, and Latin America.

**First and foremost is ensuring the safety of vaccine study subjects. Second is the safe passage of the vaccine, which is typically valued at 100 times the cost of shipping, to global trial site.**

In supplying and conducting vaccine clinical trials, sponsors and supply chain managers must maintain a twofold focus. First and foremost is ensuring the safety of vaccine study subjects.

Second is the safe passage of the vaccine, which is typically valued at 100 times the cost of shipping, to global trial sites.

## Strategy for a robust supply chain

Our strategy for establishing a robust supply chain for vaccine trials involves a rigorous process of proven durability. Ideally, planning for a vaccine clinical trial should begin approximately four to six months in advance. Thanks to our established processes and experience, however, we have and can accept projects with shorter timelines.

- Allow designers and engineers to examine the supply chain process for a specific study, making recommendations on adjustments and improvements.
- Incorporate critical Interactive Response Technology (IRT) to integrate the drug supply chain management processes of packaging and distribution with the clinical processes of patient enrollment and treatment.
- Identify secondary packaging needs once decisions about packaging and shipping have been made and IRT has been incorporated.
- Determine the need for ancillary supplies, since supplies taken for granted in Western countries may not be readily available in some emerging markets.
- Ensure that storage and distribution are sufficient in receiving sub-Good Manufacturing Practice (GMP) hub and sites.
- Evaluate the need for reverse logistics during or after the study along with destruction of unused trial supplies.
- Confirm differing temperature and handling requirements for comparator/concomitant vaccines. The recent surge in biologics testing has prompted a tightening of regulations around temperature control and monitoring.
- Address the need for analytical and stability testing, which are required by regulatory authorities.
- Double-check to be sure that labeling is correct and contains all necessary information for every region in which the study will take place. Countries differ widely in their labeling requirements.
- Consider the need for and availability of bio-repository and bio services, since laboratory tests for study subjects are standard protocol requirements.

## Planning and requirements for cold supply chain

The high cost and limited supply of vaccine have led us to develop the following flow for use in crafting a robust cold supply chain:

**Protocol → Planning → Production → Distribution**

To begin at the beginning—by thoroughly understanding the protocol and what the sponsor wishes to achieve—is critical. Failure to focus on the protocol as a starting point is much like setting out for a trip minus a destination. Thorough understanding of the protocol enables us to craft a custom distribution strategy that addresses the following key issues:

**Depots/sub-depots.** A sufficient number of depots and sub-depots ensures that product is delivered to clinical sites as needed.

**Vaccine supply.** Since vaccine is frequently in limited supply during early development, knowing when and how much product will be available is necessary for meeting tight clinical timelines.

**Kit size.** An often overlooked but critical detail is the size of the kit, which must fit easily into site refrigerators.

**Temperature requirements.** Temperature requirements impact the selection of appropriate packaging and monitoring, and ensures the product remains safe and efficacious.

**Customs/import requirements.** Customs and import requirements vary from country to country; anticipating and addressing them early in the process is critical. In nations such as China and India, customs delays due to documentation errors are commonplace and costly.

**Budget.** Establishing and adhering to a budget requires assessing the advantages and disadvantages of options with respect to cold-chain distribution and arriving at a balance between cost and risk with which both the study sponsor and the Thermo Fisher team are comfortable.

## Shipping supplies: A critical link in the supply chain

Double-digit growth in vaccine trials taking place in every corner and climate of the globe sharply raises the logistical stakes, requiring meticulous packaging and constant temperature monitoring of product shipped to clinical sites.

In reality, temperature deviations are as much of a risk for vaccine shipments bound for different regions of the United States as they are for those enroute to a different hemisphere. Consider, for example, the weather differences in cities like Boston, Phoenix, Chicago, San Diego and Seattle on a single day.

**The selection of containers and temperature monitoring are the most critical elements with respect to shipping vaccines.**

That is why every precaution must be taken to ensure safest passage from hour 1, or pack out, through delivery. Considering variables—such as potential customs delays, cancelled flights and inclement weather—is part of the process.

Even without delays, a vaccine shipment originating from the our facility in Basel, Switzerland will experience temperatures ranging from 4°C to 25°C or 39°F to 77°F during the 24-48 hour journey to a destination such as Pretoria, South Africa.

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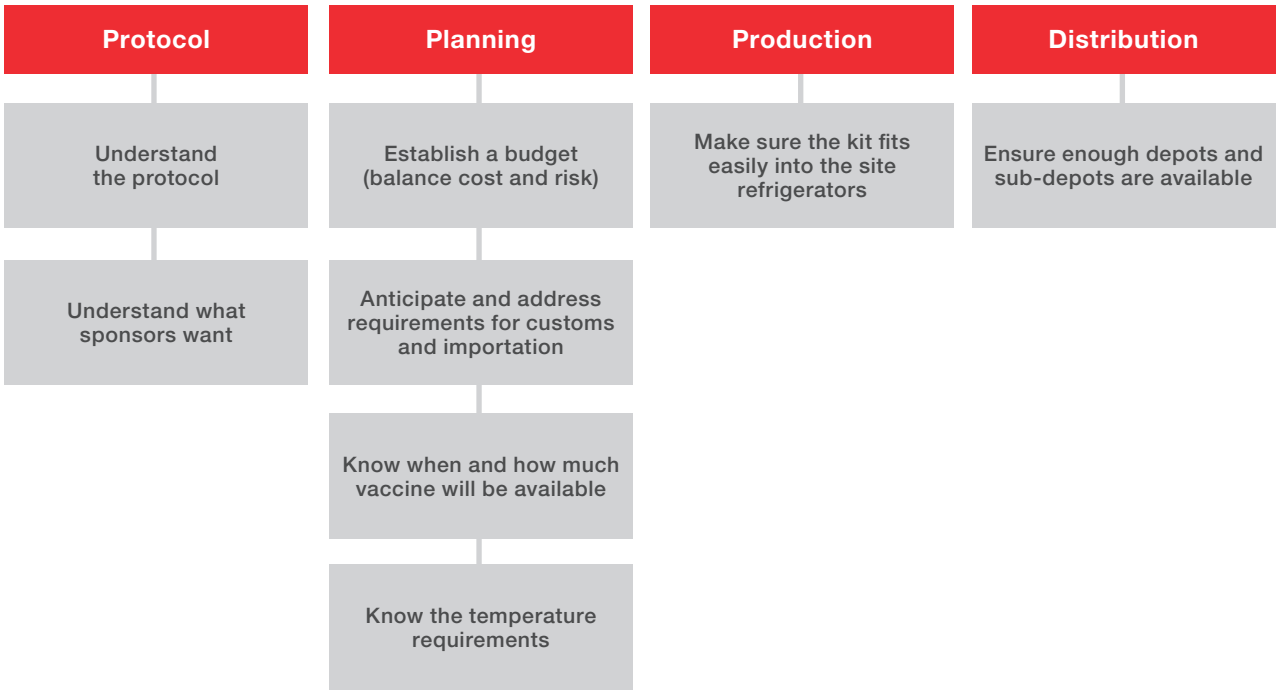
**Planning and requirements for cold supply chain chart**



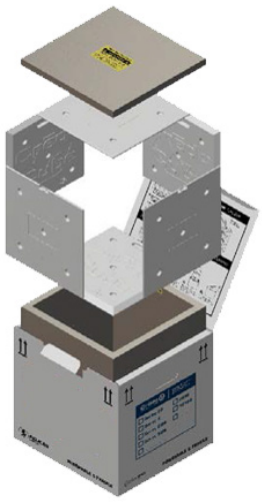

**Containers.** Manufacturers and suppliers are producing a new generation of shipping containers that incorporate new technologies, albeit at higher cost. Here are some examples:

- Phase Change Materials (PCM) function by storing and releasing energy to reduce temperature fluctuations. While this technology is costly, its use virtually guarantees that the integrity of the shipment will be un-compromised. See more about PCM in the case study that follows.
- Vacuum panels are examples of another technology used for preventing temper-ature excursions, thanks to superior insulating properties within the walls of shipping boxes. While the additional insulation enhances safety, the downside is reduced internal volume for shipments.

**Temperature monitoring.** The latest advances in temperature monitoring involve the use of Universal Serial Bus (USB) port monitors, which offer a range of welcomed advantages:

- Cost effective and small, USB port monitors can be placed as close as possible to the clinical supplies.

USB port monitors provide immediate and clear visibility of results, which can be downloaded from any personal computer (PC) to the sender. No additional software is necessary, which makes this technology useful virtually anywhere in the world where there are PCs.



The selection of containers and temperature monitoring are the most critical elements with respect to shipping vaccines.

# Maintaining regulatory standards: Impact on supply chain delivery

Patient safety is the major concern in the biopharmaceutical industry. Since many vaccines are administered to healthy people in order to prevent disease, vaccines are held to a very high standard of safety.

A vaccine that experiences temperature excursion is no longer considered efficacious and cannot be administered. Replacing discarded product is costly and often difficult, which could impact the success of a clinical development program.

That is why it is critical to meet the strict standards of Good Manufacturing Practice (GMP), Good Distribution Practice (GDP) and Good Clinical Practice (GCP) as a means of ensuring overview and control.

**Regulatory standards for clinical trials differ from region to region, so understanding them thoroughly prevents trial delays.**

It is also important to meet regulatory standards in all regions where trials are planned or underway and in which licensure is sought. This requires careful preparation, checking, double-checking and maintenance of study-related documents, a clear understanding of regulations and meticulous record keeping. Regulatory standards for clinical trials differ from region to region, so understanding them thoroughly prevents trial delays.

The requirements of the European Medicines Agency (EMA), the regulatory authority for the 27-member European Union (EU), may differ substantially from regulatory authorities in other key markets, such as the U.S. Food and Drug Administration (USFDA).

### Role of QP

In Europe, for instance, it is the responsibility of the Qualified Person (QP) to approve all aspects of manufacture, packing and labeling prior to certifying and releasing clinical supplies.

The QP must certify that the manufacture of the clinical supplies has been performed in accordance with the regulatory information submitted to the health authority, known as the Competent Authority (CA) in every country where a clinical trial will be conducted.

However, even within the EU, there will still be additional requirements for vaccine release. In Germany, for example, approval must come from a vaccine QP who is specifically trained to work and authorize release of vaccines.

The QP's statement is included in the Clinical Trial Application (CTA) submitted to every country's health authority. The CTA contains the substance of the text that will appear on the labelled clinical supplies.

## CASE STUDY

# The long road to Turkey

Weather cannot be controlled, but risk can be managed, Thermo Fisher frequently tells study sponsors. A global vaccine clinical trial conducted in 2009-2010 provides a good example of what this means and how experience, flexibility and perseverance saved the day and the trial.

Planning for the vaccine clinical development program began with initial meetings of the Thermo Fisher team and the study sponsor in May 2009. The sponsor's program was complex and aggressive, involving six separate protocols conducted simultaneously over a 12-month period, 195 sites in 11 European and Latin American countries, 250+ product shipments, and multiple-comparator/concomitant products of differing temper-ature requirements. Sub-depots were required for two countries, Argentina and Turkey.

Several trial sites were located in Turkey, a country that is a major challenge from a clinical supply chain perspective under normal circumstances. The majority of available commercial flights land in Istanbul, rather than in the capital city of Ankara, which is located about 360 kilometres or 220 miles away. As it turned out, the clinical sites were located in Ankara.

Initial shipping of clinical supplies to the first study sites began in July; however, shipping to the Turkish sites was scheduled for October 2009, shortly before the trial sites there were scheduled to begin enrollment.

As the bulk shipment was readied for packing, a period of unseasonably cold weather enveloped Europe, resulting in severe flooding in Turkey and the closure of major roads. Anticipating extended weather-related delays, we recommended a shift to a more robust Phase Change Solution for insulated shippers as a means of ensuring that temperature-sensitive clinical supplies would travel safely during what would be a 48-hour journey. The sponsor agreed and the packaging changes, though more expensive, were implemented.

In a further move to ensure safe passage, the Thermo Fisher team arranged for a specialist courier to hand carry the bulk shipment to Turkey from our facility in Basel, Switzerland via Paris. Upon arrival in Istanbul, the courier accompanied the bulk shipment through customs. The courier then organized ground transportation and accompanied the road transport from Istanbul to Ankara, a six-hour journey in unfavourable weather conditions.

**Additional details about the project:**

- The sponsor required immediate temperature monitor reading upon receipt at each site. Regardless of the time, the courier waited for the product to be unpacked, then returned to the local depot to send the temperature reading to our team the same day.
- The site shipments were divided into multiple insulated shippers with multiple readers for tracking. We designed a system to associate the monitor with the shipper, so readings were unique to the contents of the shipper.
- There was additional inventory tracking due to unspecific labeling on the Investigational Medicinal Product (IMP) and multiple lots. The Fisher Clinical Services℠ Global Project Management System (GPMS) was engaged to ensure full accountability.
- There was 24-hour turnaround of all orders, with a team trained to handle Just-in-Time (JIT) distribution. Many orders that arrived in the morning were shipped that same afternoon, often significantly under 24 hours.

The happy ending: The sites in Ankara received the supplies in time to enroll patients per schedule. The clinical development program concluded successfully in the spring of 2010, on schedule and exactly one year after the initial project meetings took place.

## Conclusion

Here are some recommendations for sponsors preparing to mount global vaccine trials:

- **Agree on a distribution strategy**—In logistics, anything is possible, but bear in mind that overcoming challenges successfully requires a partnership of supplier and sponsor.
- **Ship within a region wherever possible using qualified couriers**—We have a global footprint and expertise in shipping that is unrivalled.
- **Define a range of shippers based on a review of stability data and destination**—We use quality, qualifications and performance metrics in identifying and selecting shippers.
- **Monitor and ensure safest passage from hour 1 to delivery**—Appropriate packaging and shipping choices can spell the difference between product that maintains integrity and product that requires costly replacement.
- **Be flexible in your processes and choices**—Rely upon supply chain experts to make recommendations and changes as necessary to address developing issues and ensure safe passage of product to depots and clinical sites. Allow the experts to do what they do best.
- **Communicate clearly with all parties**—Clear communication enables supply chain managers to do the best job possible to help sponsors meet their goals.
- **Remember planning + pro-activity = success**—Whenever possible, allow four to six months for advance planning. The biggest mistake made by sponsors in preparing for vaccine trials is failing to build-in sufficient planning time.
- **Balance risk, cost, compliance and timelines**—First and foremost, remember that the safety of study subjects is the primary concern for all clinical studies.

## References

1. PhRMA Report: Medicines in Development for Infectious Diseases 2010

## About us

Thermo Fisher Scientific provides industry-leading pharma services solutions for drug development, clinical trial logistics and commercial manufacturing to customers through our Patheon brand. With more than 65 locations around the world, we provide integrated, end-to-end capabilities across all phases of development, including API, biologics, viral vectors, cGMP plasmids, formulation, clinical trials solutions, logistics services and commercial manufacturing and packaging. We give pharma and biotech companies of all sizes instant access to a global network of facilities and technical experts across the Americas, Europe, Asia and Australia. Our global leadership is built on a reputation for scientific and technical excellence. We offer integrated drug development and clinical services tailored to fit your drug development journey through our Quick to Care™ program. As a leading pharma services provider, we deliver unrivaled quality, reliability and compliance. Together with our customers, we're rapidly turning pharmaceutical possibilities into realities.

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