A **cold chain** is a temperature-controlled supply chain. An unbroken cold chain is an uninterrupted series of storage and distribution activities which maintain a given temperature range. It is used to help extend and ensure the shelf life of products such as pharmaceutical products and vaccines. Such products, during transport and when in transient storage, are called cool cargo. In other words, "Cold chain" refers to the process used to maintain optimal conditions during the transport, storage, and handling of pharmaceutical products and vaccines, starting at the manufacturer and ending with the administration of the product to the client (especially for vaccines, the optimum temperature for refrigerated vaccines is between +2°C and +8°C).

Mobile refrigeration was innovated in 1940 by Frederick McKinley Jones, who founded Thermo King.

As mentioned above, a common temperature range for a cold chain in pharmaceutical industries is 2 to 8 °C, but the specific temperature (and time at temperature) tolerances depend on the actual product being shipped. Unique to fresh produce cargoes, the cold chain requires to additionally maintain product specific environment parameter which include air quality levels (carbon dioxide, oxygen, humidity and others), which makes this the most complicated cold chain to operate.
This is important in the supply of vaccines to distant clinics in hot climates served by poorly developed transport networks. Disruption of a cold chain due to war may produce consequences similar to the smallpox outbreaks in the Philippines during the Spanish-American War.
There have been numerous events where vaccines have been shipped to third world countries with little to no cold chain infrastructure (Sub-Sahara Africa) where the vaccines were inactivated due to excess exposure to heat. Patients that thought they were being immunized, in reality were put at greater risk due to the inactivated vaccines they received. Thus great attention is now being paid to the entire cold chain distribution process to ensure that simple diseases can eventually be eradicated from society.

Traditionally all historical stability data developed for vaccines was based on the temperature range of 2–8 °C. With recent development of biological products by former vaccine developers, biologics has fallen into the same category of storage at 2–8 °C due to the nature of the products and the lack of testing these products at wider storage conditions.
The cold chain distribution process is an extension of the good manufacturing practice (GMP) environment that all drugs and biological products are required to adhere to, enforced by the various health regulatory bodies. As such, the distribution process must be validated to ensure that there is no negative impact to the safety, efficacy or quality of the drug substance. The GMP environment requires that all processes that might impact the safety, efficacy or quality of the drug substance must be validated, including storage and distribution of the drug substance.

Validation

A cold chain can be managed by a quality management system. It should be analyzed, measured, controlled, documented, and validated.
The overall approach to validation of a distribution process is by building more and more qualifications on top of each other to get to a validated state. This is done by executing a Component Qualification on the packaging components, an Operational Qualification to demonstrate that the process performs at the operational extremes and finally a Performance Qualification that demonstrates that what happens in the real world is within the limits of what was demonstrated in the Operational Qualification limits.

Performing thermal testing can also help with validating the cold chain. Certified test labs use environmental chambers to simulate ambient profiles that a package may encounter in the distribution cycle. Thermocouple probes and separate temperature data loggers measure temperatures within the product load to determine the response of the package to the test conditions. Replicate testing based on a qualification protocols is used to create a final qualification report that can be used to defend the configuration when audited by regulators. It is normally best to have an individual that understands the principles of Validation, when defending such processes to a Federal Regulatory body of any nation.
Cold chains need to be evaluated and controlled:

- Carriers and logistics providers can assist shippers. These providers have the technical ability to link with airlines for real time status, generate web-based export documentation and provide electronic tracking.
- The use of refrigerator trucks, refrigerator cars, reefer ships, reefer containers, and refrigerated warehouses is common.
- Shipment in insulated shipping containers or other specialized packaging.
- Temperature data loggers and RFID tags help monitor the temperature history of the truck, warehouse, etc. and the temperature history of the product being shipped. They also can help determine the remaining shelf life
- Documentation is critical. Each step of the custody chain needs to follow established protocols and to maintain proper records. Customs delays occur due to inaccurate or incomplete customs paperwork, so basic guidelines for creating a commercial invoice should be followed to ensure the proper verbiage, number of copies, and other details.

During the distribution process one should monitor that process until one builds a sufficient data set that clearly demonstrates the process is in compliance and in a state of control. Each time the process does not conform to the process, the event should be properly documented, investigated and corrected so that the temperature excursion do not occur on future shipments. Any anomaly is thus considered to be a Non Conformance and should be assigned as a tractable event. The event must be reported immediately when it is identified and it is the expectation of the FDA that all adverse events to documented and investigated. The investigation should be completed in a timely manner and must come to some form of a "root cause" and also some form of "corrective action". The system may potentially stay in a validated state if the root cause identifies that a Standard Operating Procedure (SOP) was not followed or followed incorrectly. If however a SOP needs to be changed or modified, then the system must be re-validated to demonstrate that the change to the SOP maintains the integrity of the process/system. A Non-Conformance may also generate a Corrective Action Preventative Action (CAPA), again, a documented process to make corrective or preventative actions to SOP's and other documents.
Non Conformances and CAPA's are an essential part of the overall Quality System in the cGMP environment. Tracking and trending of these events will also allow businesses to monitor the overall "health" of the systems in place. Excessive Non Conformances can quickly identify areas of concern for management and allow for corrective actions to be takes. During regulatory inspections of quality systems, inspectors will frequently ask to review a list of all "open" Non Conformances" so that they can quickly assess how an organization is processing these events and ensuring they are dealt with in a timely manner.
Thus the process is continually evolving and correcting for anomalies that occur in the process. Eventually the process can evolve into periodic monitoring once sufficient data demonstrates that

the process is in a state of control. Any anomaly that occurs once a process is in a state of control may result in the process being invalidated and not in control and could potentially result in product withdraw from the market to ensure patient safety. A formal product withdraw is only done when the quality, safety or efficacy of a product is questionable. A single anomaly would not necessarily require a product withdraw if there is sufficient stability data that demonstrates that excursions will not affect product quality.
It is necessary to develop an internal documentation system as well as multi-party communication standards and protocols to transfer or create a central repository or hub to track information across the supply chain. These systems would monitor equipment status, product temperature history, and custody chain, etc. These help ensure that a food, pharmaceutical, or vaccine is safe and effective when reaching its intended consumer. It is also important to have a complete chain of custody for the entire life cycle of a product, so there is documented evidence as to whom had control of the product throughout the lifecycle of the product, up to the final users' consumption of the product.

Especially for vaccines

Vaccines are sensitive biological products which may become less effective, or even destroyed, when exposed to temperatures outside the recommended range. Cold-sensitive vaccines experience an immediate loss of potency following freezing. Vaccines exposed to temperatures above the recommended temperature range experience some loss of potency with each episode of exposure. Repetitive exposure to heat episodes results in a cumulative loss of potency that is not reversible. However, information on vaccine degradation is sparse and multipoint stability studies on vaccines are difficult to perform. In addition, information from manufacturers is not always available, so it can be difficult to assess the potency of a mishandled vaccine.
Maintaining the potency of vaccines is important for several reasons.
There is a need to ensure that an effective product is being used. Vaccine failures caused by administration of compromised vaccine may result in the re-emergence or occurrence of vaccine preventable disease.
Careful management of resources is important. Vaccines are expensive and can be in short supply. Loss of vaccines may result in the cancellation of immunization clinics resulting in lost opportunities to immunize.
Revaccination of people who have received an ineffective vaccine is professionally uncomfortable and may cause a loss of public confidence in vaccines and/or the health care system.
An estimated 17% to 37% of healthcare providers expose vaccines to improper storage temperatures. Refrigerator temperatures are more commonly kept too cold rather than too warm. One study involving site visits showed that 15% of refrigeration units had temperatures of +1°C or lower.
Temperatures falling outside the recommended range require immediate action to avoid loss of product.
When a cold chain break is identified after a vaccine has been administered, consult your local public health office or immunization program* for advice. The type of vaccine, duration and temperature of the exposure will be taken into account when assessing the situation. Serological testing or revaccination may be suggested.
Vaccines are sensitive biological products that may become less effective, or even destroyed, when exposed to temperatures outside the recommended range and/or on exposure to direct sunlight or fluorescent light.

Ktemp®
Innovative Solutions in Cold Chain

References

- Wikipedia
- Public Health Agency of Canada