INTRODUCTION

Cold chain management is the specialist area of the pharmaceutical and biopharmaceutical distribution dealing with products that are required to be held and distributed in a controlled environment. Concerns over having adequate control in cold chain are increasing, mainly because:

- Increasing volumes of cold products in the supply chain
- Complexity of cold product (e.g., new types of product, patient specific products)
- Complexity of the supply chain (worldwide supply)

Therefore, it is considered critical to have adequate control of all steps and procedures involved both in manufacturing and quality control and in storage and distribution, to ensure that product quality is maintained.

DISCUSSION

The pharmaceutical distribution chain\(^1\) (Fig 1)

At every point in the chain, precautions should be taken to minimise the effect of external conditions on the quality and stability of the product. It is mandatory that records should provide reliable up-to-date evidence of compliance, in case of audits and investigations. Before setting up a storage facility, transport system or taking on a new range of products, it is advisable that distributors carry out a risk analysis.

![Fig 1: The Pharmaceutical Distribution Chain](image-url)
Cold storage [10,15,11]

Low volume
Domestic refrigerators may be suitable for cold storage of small volumes of some products, for example eye drops, which require cold storage but are less susceptible to being out of the recommended temperature range. The minimum requirement for monitoring is a max/min thermometer. This should be placed within the load and positioned so that opening and closing of the door will not affect the readings. The thermometer should be read and reset daily and the maximum and minimum temperatures recorded. Care should be exercised when placing goods in domestic units. If placed next to or in contact with the chiller plate or coil, their temperature may fall below the recommended minimum. Because domestic refrigerators lack the precise temperature control and uniformity, continuous recording should be considered. Thermal mapping is also advisable to determine cold and warm locations over a period of time.

High volume[2]
Large refrigerators (in excess of 6 m³) and walk-in cold rooms used in high-volume operations should be fitted with an electronic temperature recording device that measures load temperatures.

- The facility should be fitted with a power-failure alarm
- Portable data-loggers, which can be downloaded onto a computer, may be used instead of a fixed device, though the system should allow temperatures to be seen/alarmed at all times.
- The internal air temperature distribution should be mapped on installation in both the empty and full state. Air temperature distribution should be checked annually under conditions of normal use.

Walk-in units[3]

- Temperature mapping should be repeated if significant changes take place, such as the repair or replacement of the refrigeration unit or changes to the internal storage layout.
- A calibrated max/min thermometer should be placed inside the unit for use as a back-up and to confirm the temperature indicated on the recorder.
- Goods sensitive to temperatures greater than 8°C should not be stored next to the door and goods susceptible to temperatures below 2°C should not be placed in the airflow from the refrigeration unit
- Probes should be sited within an appropriate load simulator so that transient rises in temperature (such as might occur when a door is opened) do not trigger the alarm
- The low-temperature alarm must trigger before the temperature drops below +1°C
- Condensate from chilled units should not be collected inside the cold store in an open vessel
- Consideration can be given to the monitoring of relative humidity (RH) within the facility

Freezers[4]
A small but increasing number of products must be stored frozen (e.g. some blood products and products of biotechnology). These will be labelled store below -5°C (freeze) or below 15°C (deep freeze) or they may show a range (e.g. -15°C to -20°C). Storage units must be capable of maintaining the required temperature in all parts of the load, and temperatures should be monitored within the load and recorded daily.

Cool storage[4]
A small number of medicinal products are labelled ‘store in a cool place’ or ‘store between 8°C and 15°C’. If a facility operating within this range is not available, advice is that the goods may be stored at 2°C-8°C, provided that storage below 8°C does not affect their physical stability. Otherwise they should be stored in the coolest part of the warehouse and temperature monitoring should be regularly carried out.

Controlled room temperature storage[5]
Unless stated otherwise, the majority of medicinal products can be stored under conditions of controlled room temperature. These products are usually labelled ‘do not store above 25°C’. For these products room temperature extremes of hot and cold temperature must not be encountered. The minimum requirement for temperature measurement is that a max/min thermometer be placed at a strategic location and read, recorded and reset regularly and measured at both low and high levels. Warehouses should be temperature mapped to determine the temperature distribution and Mapping should be repeated every 2-3 years.

Calibration of measuring devices[8]
Manual and electronic measuring and recording devices used in critical areas and with high-risk goods should be calibrated at least annually against a traceable reference device. Records should include pre- and post-calibration readings and details of any adjustments made.

Mapping and Monitoring Equipment[12]

i) Sensors

Temperature: 3 main types of temperature sensors include:
- Thermocouples: Thermocouples work due to seebeck effect- when a conductor is subjected to a temperature gradient, it will generate a voltage. This voltage is then measured.
- Resistance Temperature Detectors (RTDs) and Thermistors: They are available to various grades and manufactured for a variety of housings. High quality sensors are considered reliable and accurate and may last more than eight years in accelerated tests, while maintaining the specified accuracy.

The accuracy of an RTD is defined by its class according to the International Electrotechnical Commission (IEC) publication 751; it is affected by the operating temperature:
- A class A device will be within ±0.15 degrees C at 0°C (±0.27 degrees F at 32°F)
- A class B device will be within ±0.3 degrees C at 0°C (±0.54 degrees F at 32°F)

Chemical: There are chemicals that change in colour depending on the temperature. These indicators can be used to record the minimum and maximum temperatures. These devices are not considered accurate and normally there is no time record associated with temperature change.
Humidity
There are two common types of humidity measurement sensor in use:

a) Capacitative units:
These are based on measuring the change in capacitance between two plates as the humidity level between the plates changes.

b) Resistive units:
These devices measure the change in resistance of a polymeric membrane. Accuracy of ±1% RH are readily available in commercial equipment; accuracies of up to ±0.5% RH are also available in higher grade equipment.

ii) Recording devices
These may be single use or reusable individual data loggers. e.g.: Elpro, 3M TL 30. There are other devices that may be used to provide the data in a number of formats to facilitate analysis. E.g.: validator 2000.

iii) Real Time Monitoring and Recording Devices
These are radio transmitters that transmit the data from local sensor to a base station allowing real time monitoring, recording, and analysis of the data. Current data recorders are a number of formats to facilitate analysis. E.g.: validator 2000.

Implementing Cold Chain at Primary Level

a) Receiving Stocks at Warehouse / CFA
- Check the Shipment for any outer damage and mention appropriate remarks on the Docket.
- Check the Vaccine for appropriate temperature at the time of receipt.
- Move Stocks Immediately to Cold Storage Facility.
- Counting/Segregation to be done in the ANTE ROOM preferably.

b) Storage of Stocks at Warehouse / CFA
- Readings taken every-day after every 3 to 5 minutes intervals. Prefer Automated System.
- Maintain Deviation SOP’s & Register
- Have appropriate Backup Facility

Implementing Cold Chain at the Secondary/ Tertiary Level

Controls could be brought at 3 Levels:

a) Selecting a Cold Chain Stockist
- Ensure the Stockist has a Walk in Cooler / Cold Chain Facility and Adequate Knowledge on Cold Chain Product Handling
- Get the stockist sign a Quality Agreement / Undertaking.

b) Educating the Stockists
- Use refrigerators – that would best suit your stocks.
- Have appropriate Warning Signage (In Local Language) & Plug Guards.
- Have separate temperature controls.
- Avoid keeping items other than high risk products (vaccines) in the refrigerator.
- Do Not Store 2 to 8 °C stocks in the Freezer / Top Shelf.
- Arrange the boxes of Vaccine in Stacks between which the air can move.
- Keep Ice Packs in the Top and Bottom Shelves – They help to keep the temperature constant.

Fig 2: Example label to be affixed to shipment boxes to alert handling to maintain the cold chain.
VVM (Vaccine Vial Monitoring): (Fig 3)
- This is printed on the label of the Vial / Cap.
- As the vial is exposed to more heat, the vial becomes darker and darker.
- Return these vaccines at the earliest.

Freeze Watch Indicators: (Fig 4)
- It consists of a small vial of red liquid attached to a white card & covered in plastic.
- The vial breaks if the temperature near the indicator drops below 0°C for more than 1 hour.
- Manufacturers pack temperature indicators with DTP & TT vaccines to monitor them during transportation & Storage.

Vaccine Cold Chain Monitors (CCM)
- These are Cards that changes colour when the vaccine is exposed to temperatures that are too high. Health Workers use them to estimate the length of time – the vaccine was exposed to high temperature.
- Companies use these monitors with the BCG, DTP, polio and measles vaccines supplied by WHO/UNICEF.

Phase Change Systems
These materials can be natural, such as ice or dry ice. The engineered Materials can be specified to change phase at a precise temperature to suit the product or package. e.g., -40°C. The phase change materials may contained within hollow panels providing re-usable sections that fit together to form a box. The box may be placed in an insulated outer container.

Fig 3: Vaccine Vial Monitoring.

CONCLUSION
The standardised use of good cold chain management practices (GCCMP) will be beneficial for all involved parties in handling, storing and distributing environmentally sensitive pharmaceuticals. An on-going monitoring programme will provide data to make the quality decision for each shipment. Regulatory guidance and inspectional trends demonstrate a focus on Good Cold Chain Management Practices. All partners should have the distinct common goal ensuring that patient and site is supplied with the correct medication at the right time and in the right condition.

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