P05: Pharmaceutical Cold Chain

E356 Pharmaceutical and Bio-Chem Supply Chain

Diploma in Supply Chain Management (DSCM)

E356 Topic Tree

Pharmaceutical and Bio-chem Supply Chain

- Introduction to Pharma and Bio-chem
- Classification of Dangerous Goods
- Best Practices (GMP/GDP)
- Clinical Supply Chain
- Cold Chain Management

Import, Packaging and Distribution

- Import and Distribution of Medical Devices
- Import of Pharmaceutical and Bio-Chem Products
- Local Transportation of Pharmaceutical and Bio Chem Products
- Packaging of Pharmaceutical DG for Air Transport
- Declaration of Pharmaceutical DG for Air Transport

Product Tracing, Recall and Disposal

- Product Tracing
- Drug Recall
- Disposal of Bio-chem Products in Hospital Logistics

Cold Chain for Pharmaceuticals

- 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.
- Cold Chain has begun to play an increasingly critical role in pharmaceutical development processes.
- It defines how temperature-sensitive substances are packaged, transported and stored throughout the R&D cycle and the supply chain.
- Temperature-sensitive biomaterials (clinical trial samples, tissue samples, APIs, viral samples etc.) play a vital role in bringing new drugs to market.
- During transit and storage they must be handled carefully at all times to maintain their cold or frozen state and meet regulatory guidelines.

Relevant Industrial Guidelines in Cold Chain for Pharmaceuticals

Recommended industry guidelines

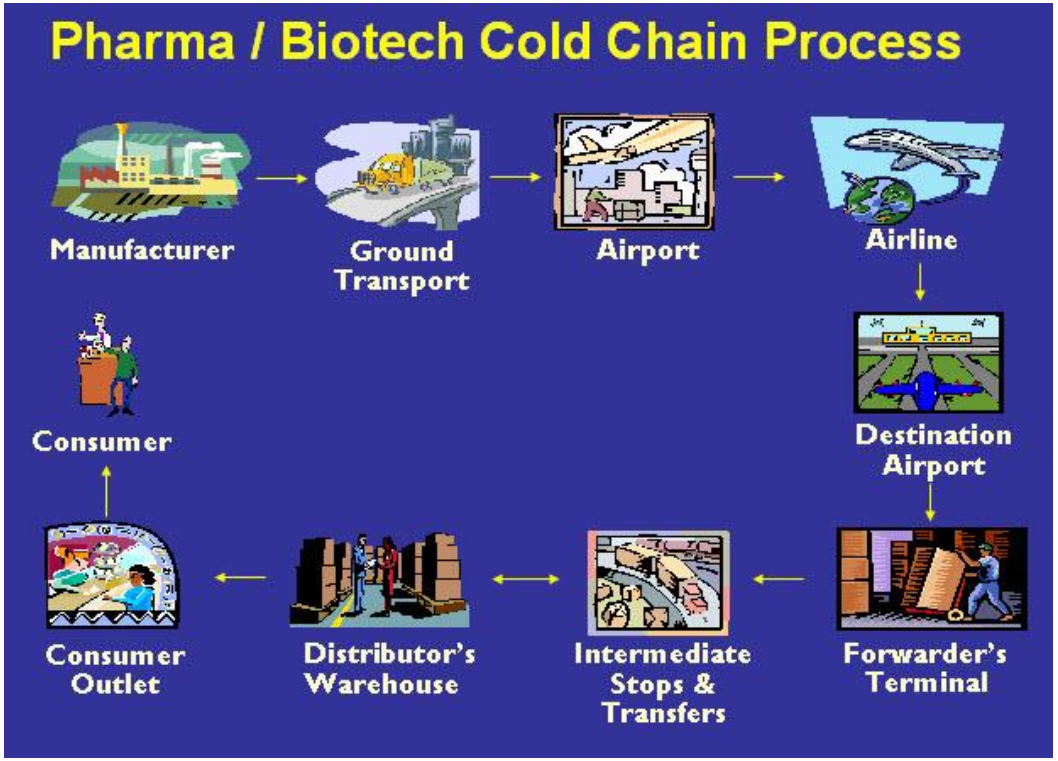
- **Good Manufacturing Practices (GMP)**
  – guidelines for manufacturers to ensure quality of product
- **Good Distribution Practices (GDP)**
  – guidelines to ensure products are stored, transported and handled in suitable conditions
- **Good Clinical Practice (GCP)**
  – guidelines on how clinical trials should be conducted
- **Good Cold Chain Management Practices (GCCMP)**
  – a set of good storage and shipping practices for temperature-controlled products

Managing the Cold Chain Logistics

Current Cold Chain Logistics has many handover points

- 3PL storage facilities
- Courier / Freight Forwarder / Transportation Companies
- Airlines / Ground Handlers / Aircraft
- Customs

Each point is a potential area for mishandling

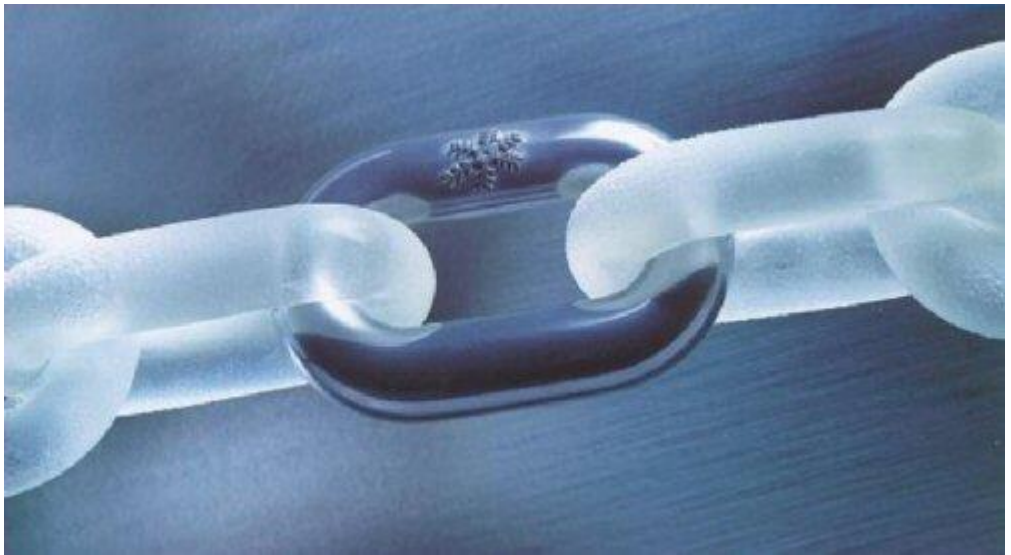


Factors affecting Cold Chain

- **To mitigate both financial and legal risk, pharmaceutical companies must implement standard operating procedures and comply with complex regulations that may not necessarily apply to the traditional supply chain.**
- **Specific factors that should be considered include:**
  - Training & Compliance
  - Packaging
  - Temperature Monitoring Devices
  - Labelling & Documentation
  - Air Transportation
  - International Shipping

Risk Management in Cold Chain Logistics

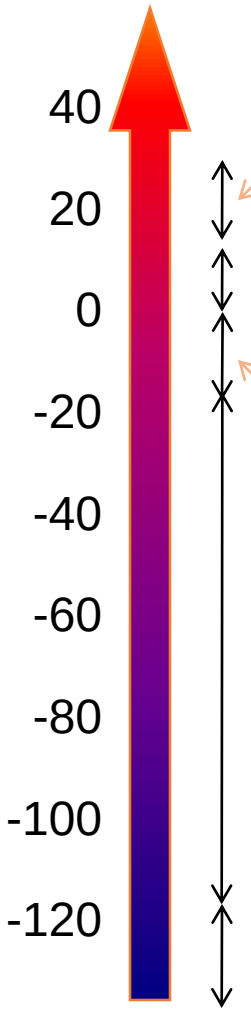
- Anticipate / Identify Critical Control Points (CCP) in Cold Chain logistics and conduct risk assessment
- Critical Control Points are where the risks are the highest
- Develop Risk Control strategies for identified risks
- Ensure that this is communicated to all parties
- Build in a Risk Review cycle



Critical Control Points in Cold Chain

- ✓**Thermal Packaging Systems**
- ✓**Qualified Packaging – Understanding the Variables**
- ✓**Training**
- ✓**Managing Cold Chain Shipments**
- ✓**Customs Clearance**
- ✓**Contingency Planning**

Temperature Range Terminology



+15°C to +25°C **Controlled Room Temperature** / Controlled Ambient
e.g. investigational drugs, prescriptive drugs e.g. Lipitor

+2°C to +8°C **Chilled**
e.g. drug ingredients and compounds, vaccines

0°C to -18°C **Freezing**

-18°C to -118 °C **Deep freezing**
e.g. Biological samples for Pharmacokinetics testing

-118°C and below - **Cryogenics**
e.g. embryos, stem cells

Packaging for different temperatures

- **Proper packaging is essential to maintaining integrity throughout the cold chain process**
- **Validated packaging and effective packing techniques will protect products during transit and unexpected delays**
- **When communicating temperatures, the 2 critical information must be clear:**
  - Positive or Negative temperature e.g. +6 °C or -6 °C
  - Celsius (°C) or Fahrenheit (°F)

To convert between °C and °F,

Celsius to Fahrenheit	$(°C \times {}^{9}/_{5}) + 32 = °F$
Fahrenheit to Celsius	$(°F - 32) \times {}^{5}/_{9} = °C$

e.g. 0°C = 32°F and 0°F = -18°C

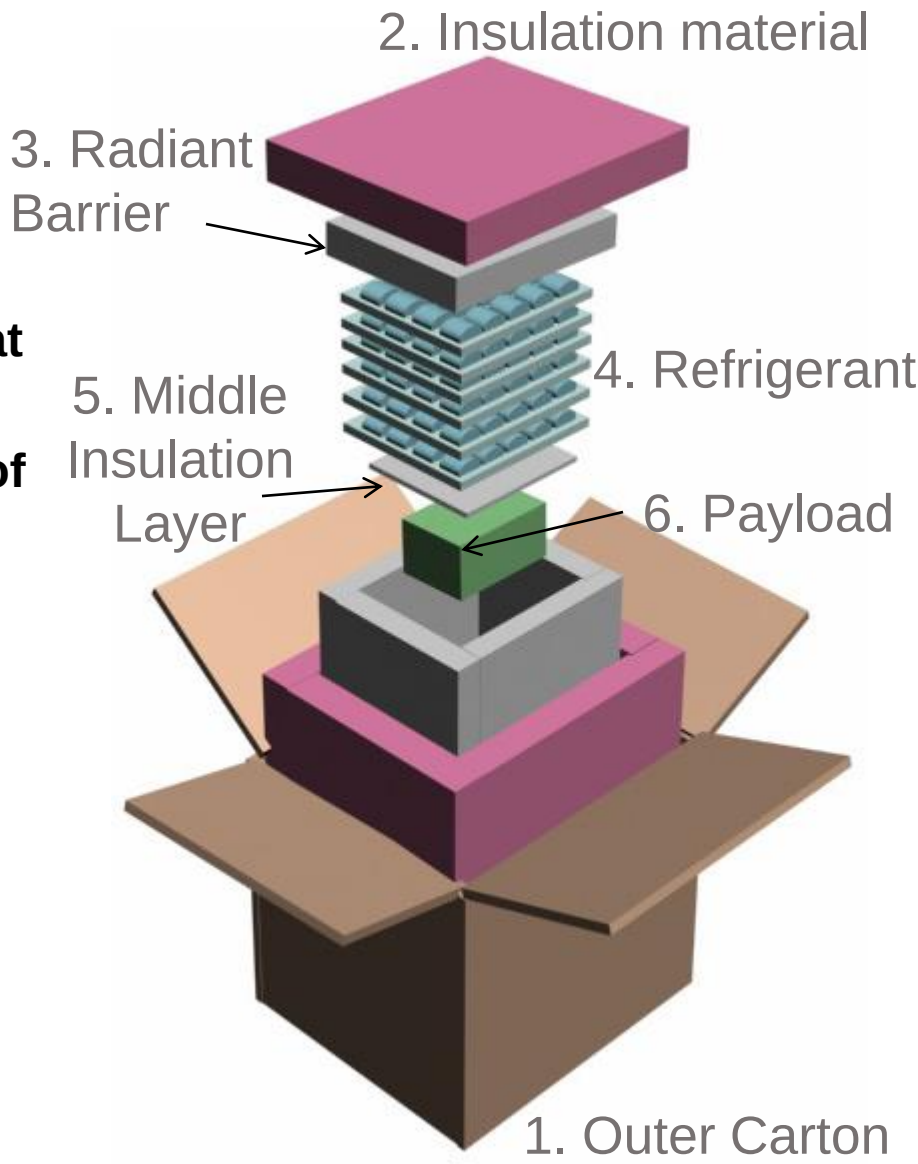
Packaging for chilled / controlled room temperature shipments

- For biological substances that must be maintained between at +2°C to +8°C and +15°C to +25°C, packaging must be properly pre-conditioned prior to shipment.
- Pre-conditioning helps the packaging maintain its rated temperature for the optimum amount of time.
- Compliant packaging is irrelevant if it is not properly prepared before its temperature-sensitive contents are inserted.

Typical Shipping System (chilled / controlled room temperature)

A single-use cold chain shipping system commonly consists of the following parts:

1. **Outer Carton – to protect and hold the items inside, labeling**
2. **Insulation material – to minimize heat absorbed from the surrounding**
3. **Radiant Barrier – to reduce effects of radiation**
4. **Refrigerant – cooling substance to absorb the heat that has traveled from the surrounding in.**
5. **Middle insulation layer – to separate the payload and the refrigerant and reduce radiation effects**
6. **Payload – product to be shipped**



Interpreting the Performance Reports

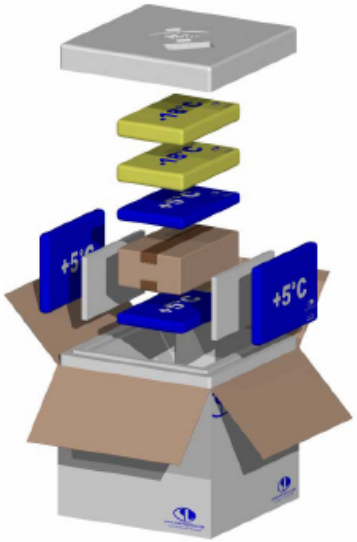
Supplier of cold chain shipping boxes will provide product performance summary of the various shipping systems, in order to select the appropriate ones

www.sca-cool-logistics.com

T1677-6 Performance Summary

72 hour winter (SE Asia) system – 4.5L product load

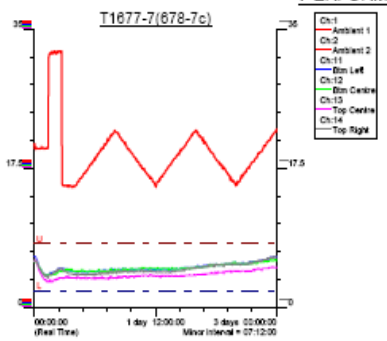
System Diagram



Temperature Controlled Shipping System

+2°C to +8°C

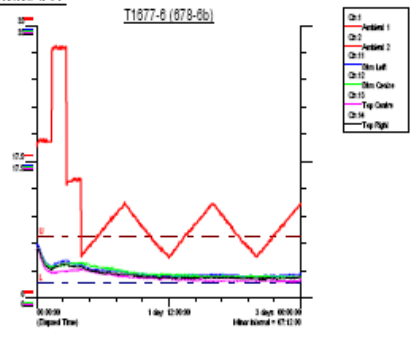
Performance Summary



Winter Upper

Ambient Temperature Profile
20°C for 4 hours, 32°C for 4 hours,
15°C for 4 hours,
15°C to 22°C ramped over 12 hours,
22°C to 15°C ramped over 12 hours,
Repeat 22°C to 15°C ramped profile

Results
Product temperature:
2°C to 8°C for 72 hours, 00 minutes +
Maximum product temperature was 6.4°C @ 00:00
Minimum product temperature was 3.2°C @ 03:40



Winter Lower

Ambient Temperature Profile
20°C for 4 hours, 32°C for 4 hours,
15°C for 4 hours,
5°C to 12°C ramped over 12 hours,
12°C to 5°C ramped over 12 hours,
Repeat 12°C to 5°C ramped profile

Results
Product temperature:
2°C to 8°C for 72 hours, 00 minutes +
Maximum product temperature was 6.9°C @ 00:10
Minimum product temperature was 2.1°C @ 54:40

Bill of Materials

1x CL7725 EPS Moulding (base and lid)
1x Printed Cardboard Outer Carton
4x WS3020 Cool-Pacs @ +5°C
2x WS3020 Cool-Pacs @ -18°C
2x EPS Spacer (300x160x15mm)
1x Inner Carton (300x180x85mm)

System Specification

CL7725 Dimensions

External Dimensions:	456 x 456 x 386mm
Internal Dimensions:	320 x 320 x 245mm
System Weight:	11.2kg
Volumetric Weight:	13.4kg

Product Space: 300 x 180 x 85mm (4.5 litres)

Conditioning time of frozen CoolPacs prior to assembly: 20 minutes

Packaging for Frozen Shipments

- Dry ice and liquid nitrogen are commonly used to ship biological materials that must be maintained in a frozen state
- Often, logistics personnel are unfamiliar with best practices that should be followed when using these sub-zero substances to maintain the integrity of perishable biological materials
- The frozen shipments can be classified under 3 negative temperature groups, namely
  - Freezing
  - Deep Freezing
  - Cryogenics

Packaging for Frozen Shipments

Cryogenics

Refrigerant & Apparatus: Liquid Nitrogen whose normal temperature is

-196°C, where it can be used as Wet Shipper (N_2 sits in metal cylinder like water in a bucket) or Dry Shipper (with a foam lining in the cylinder to absorb the N_2)

Deep Freezing

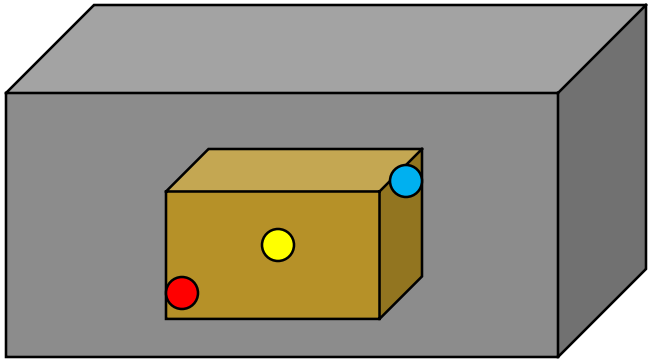
Refrigerant & Apparatus: Dry Ice, which usually has a temperature of -79°C, accompanied by insulated packaging

Freezing

Refrigerant & Apparatus: Gel packs and packaging systems, with the gel packs designed to perform at specific temperatures

Temperature Monitoring Devices

- **Besides selecting the proper packaging and using it correctly, there are additional methods that logistics personnel can utilize to confirm that the packaging maintains the contents at the desired temperature throughout shipments, e.g. by using temperature data loggers**
- **The common practice is to use 1 data logger to measure 1 point of the product area, but the minimum recommended number is 3 (especially for qualification)**
  - 1 at upper corner of product area
  - 1 at centre of product area
  - 1 at lower corner of product area



IoT in Pharma Cold Chain

Temperature Data Loggers

- **Small enough to travel with small cartons to record temperature during the passage**
- **Can be of single or multiple use, with or without display**
- **Usually programmable through software interfaced to PC**
- **Temperature profile can be downloaded for analysis**

Single-use disposable temperature logger

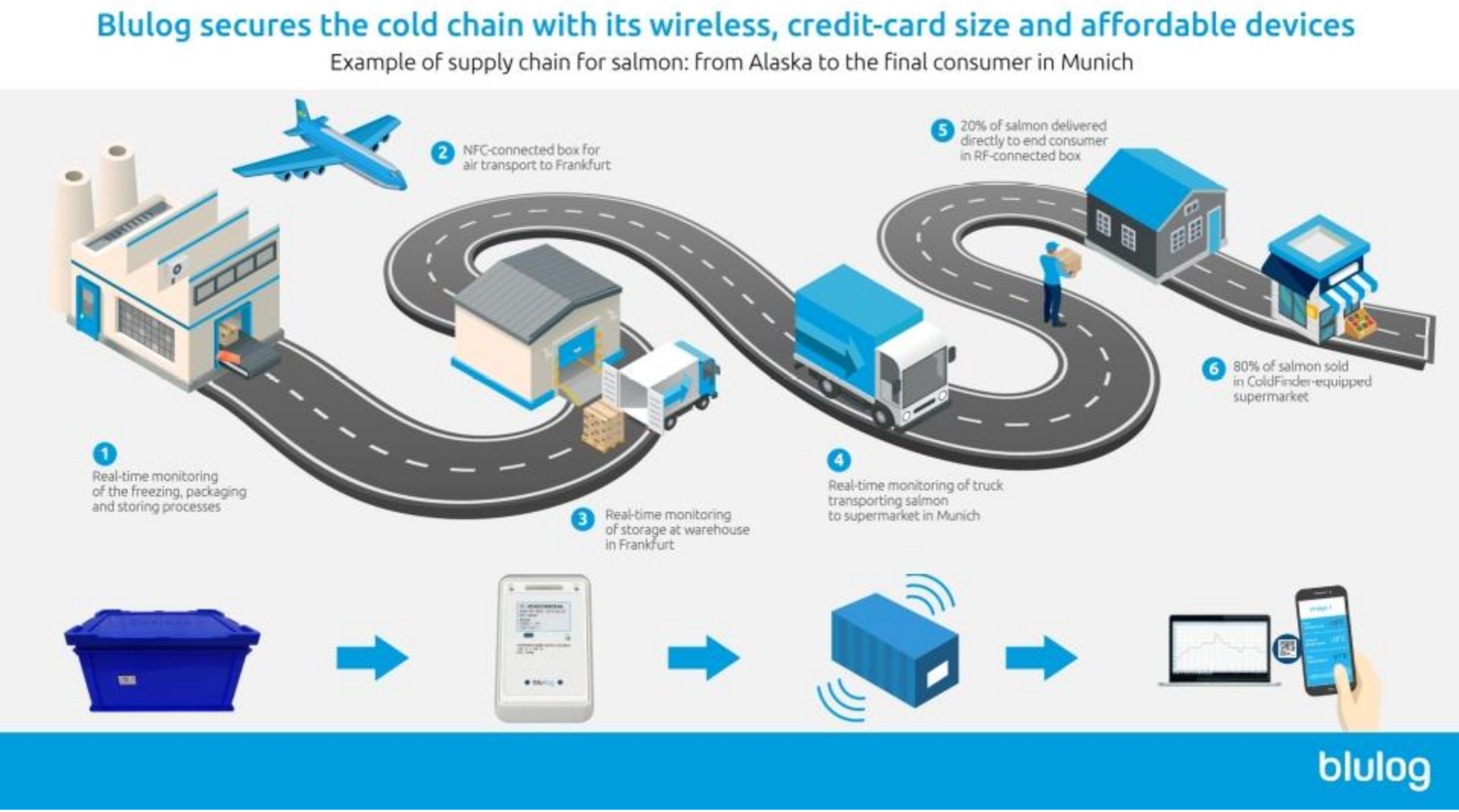
Multiple use temperature logger

Semi-passive RFID tags with capability of logging temperature

Tag Sensor NFC Dataloggers (External and Internal)

https://youtu.be/2ogSxZPRQqw

Blulog NFC dataloggers (Internal)



Time Temperature Indicators (TTI)

Indicators are for single-use, they give a quick indication on temperature excursions but do not give details of when it happened.

Freeze tags – shows on display if there has been an exposure of below 0°C for over 10 minutes

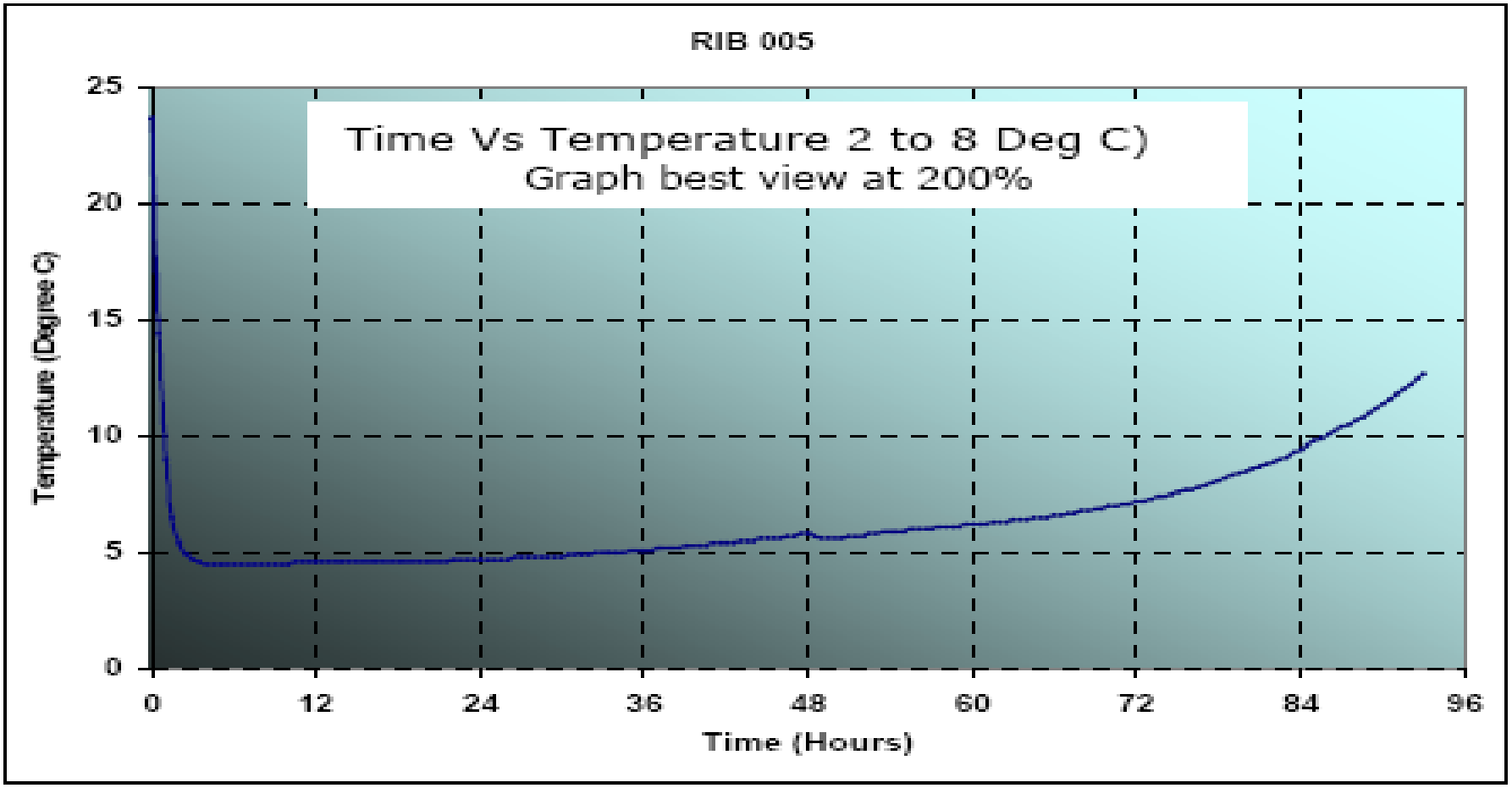
Exposed to temperature above 0 deg C after 30min

Exposed to temperature above 0 deg C after 4hrs

Exposed to temperature above 0 deg C after 12hrs

WarmMark indicators monitor whether a product has been exposed to temperatures above a pre-determined threshold as a red dye is released to indicate the duration

Typical temperature profile in 72 hours



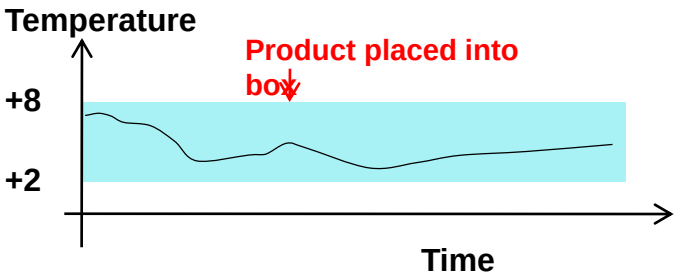
The above graph demonstrates how temperature maintains between 2 to 8 deg. C for up to 80 hours under controlled ambient temperature of 28 ~ 30 deg. C. The test conducted using temperature recorder placed inside the overpack.

Pre-shipment monitoring

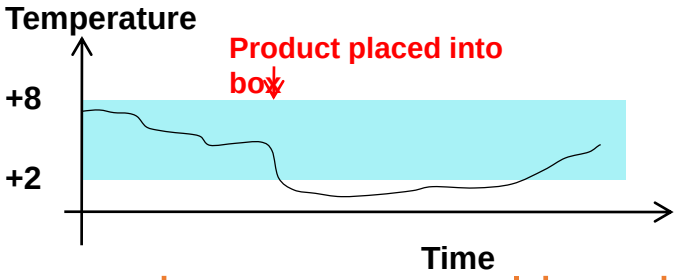
A beneficial technique for ensuring that a box has been set up correctly is to do pre-shipment monitoring, e.g.:

- Prepare and final condition gel packs 2.5hrs prior to the expected packing time of the shipment
- Pack the boxes and start monitoring the temperature 2hrs before product is placed in the box
- After 2hrs & before placing the product in the box, check the temperature
  - If the box is at the correct temperature, place the product in
  - If the box is not at the correct temperature, delay the packing until the temperature is correct, or abort the process
- As soon as the product has been placed into the box, note down the time and from the graph that has been downloaded, check if the box or product has been conditioned correctly

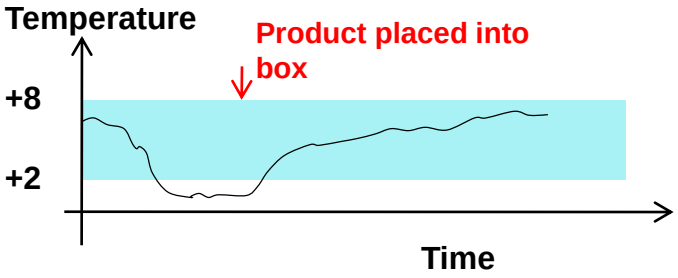
Examples of Shipment monitoring graphs



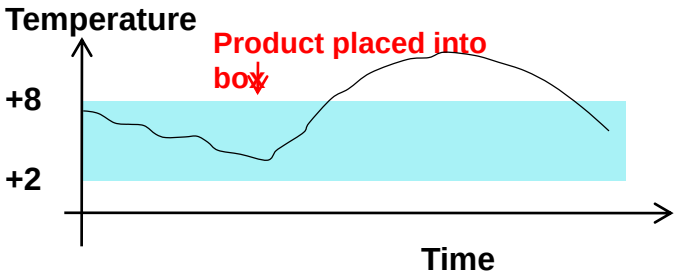
- **The refrigerants were set up correctly, and the product was of the correct temperature**



- The product was too cold, and caused the temperature in the box to fall below **+2ºC**

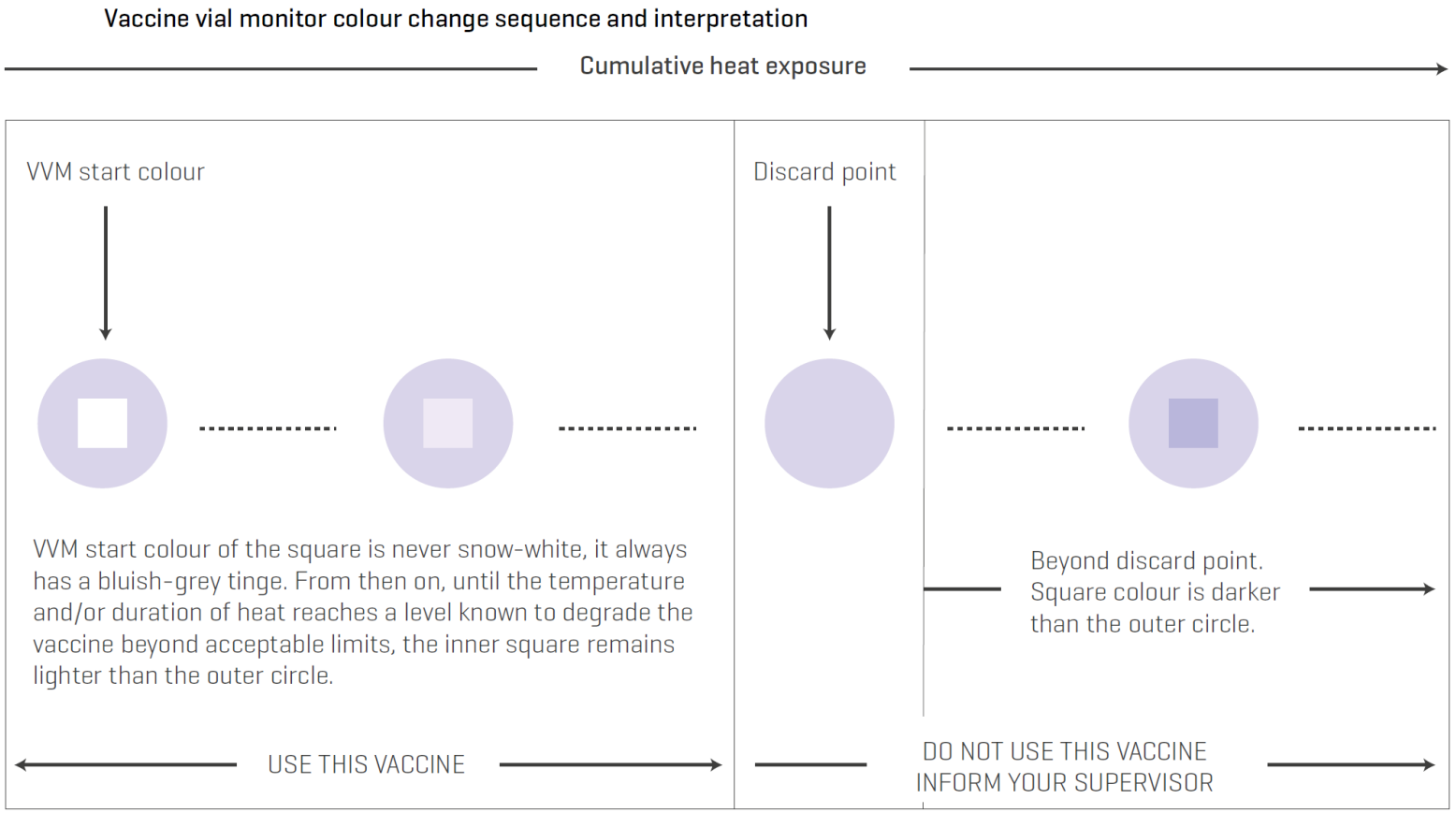


- The refrigerants were not prepared correctly, and dropped below +2ºC before product was placed in



- The product was too hot, and caused the temperature in the box to rise above **+8ºC**

Today's Problem – Vaccines Vial Monitor



VVM colour change is a continuous process. The combined effects of time and temperature cause the inner square (active surface) of the VVM to darken gradually and irreversibly. The rate of colour change increases with temperature. The inner square is initially lighter in colour than the outer circle (but the inner square is never white). It remains so until the temperature and/or the duration of heat reaches a level that is likely to degrade the vaccine beyond the acceptable limit. The inner square continues to darken as heat exposure continues, until it is much darker than the outer circle.
If the inner square becomes as dark as or darker than the outer circle the vial must be discarded.
Therefore the whole interpretation of whether to use the vaccine depends on whether the inner square is lighter than the outer circle.

Source: From WHO Vaccine Management Handbook

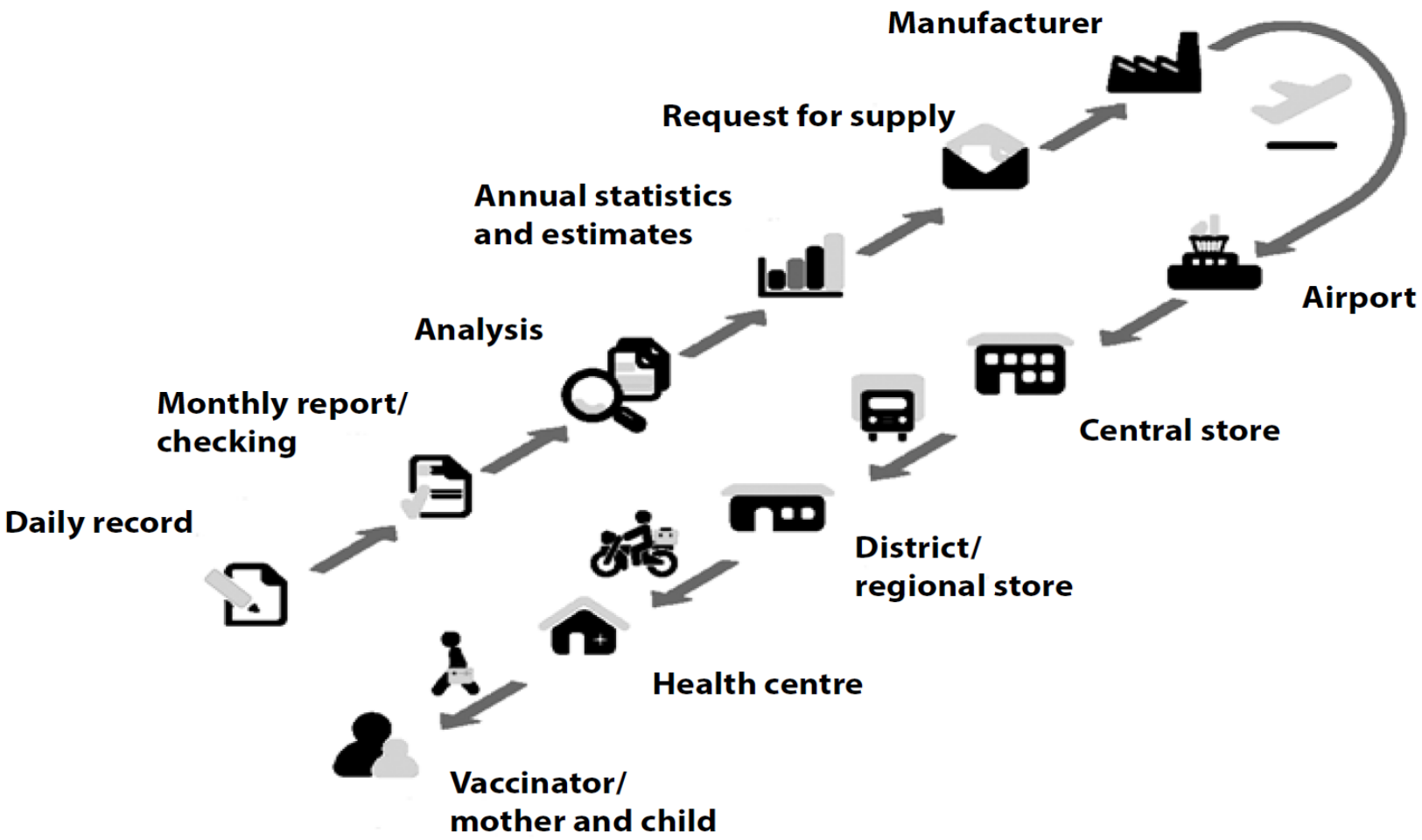
Today's Problem – Causes of Vaccine Heat and freeze exposure

Some common causes of vaccine heat and freeze exposure

Causes of heat exposure	Causes of freeze exposure
During storage	
• Electrical power failures causing breaks in the cold chain. • Lack of fuel (gas or kerosene) for refrigerators used in areas with no electricity. • Cold chain equipment breakdown. • Storing vaccines in nonmedical cold chain equipment like domestic refrigerators or freezers which are not designed for this purpose.	• Storing freeze-sensitive vaccines close to cold room refrigeration units or in other cold spots such as the dividing wall between a freezer room and a cold room. • Incorrect thermostat adjustment in cold rooms and refrigerators with adjustable thermostats. • Failure to use the baskets supplied with ice-lined refrigerators/ allowing freeze-sensitive vaccines to be stored outside the manufacturer's designated safe storage zone. • Storing freeze-sensitive vaccines in domestic refrigerators in close proximity to the evaporator plate.
During transport	
• Passive container packed with too few or inappropriately sized coolant packs. • Delivery or outreach trips exceeding the passive container's cold life. • Vehicle breakdown. • Refrigeration system breakdown (refrigerated vehicles). • Parking vehicles in direct sunlight.	• Packing freeze-sensitive vaccines in passive containers with unconditioned ice-packs. • Transporting freeze-sensitive vaccines in refrigerated vehicles that are poorly maintained and/or incorrectly packed. • Transporting freeze-sensitive vaccines incorrectly in countries with very low winter temperatures.
During immunization sessions	
• Exposure of vaccines to high ambient temperatures during immunization sessions.	• Not applicable.

Source: From WHO Vaccine Management Handbook

Today's Problem – The Vaccine Cold Chain



Source: From WHO Vaccine Management Handbook

Today’s Problem - Recommendation

- Pharmaceutical & Bio-chem products are typically very sensitive to temperature conditions, and can lose its potency when conditions are not optimal.
- To maintain the quality of the Pharmaceutical & Bio-chem products, a validated cold box that can maintain its internal temperature within the specified temperature range for a specified shipment time frame should be used.
- The refrigerants of the cold box must be properly conditioned, and the product must also be maintained within the temperature range when it is packed.

Today’s Problem - Recommendation

- Temperature loggers have to be placed inside the box and used for pre-shipment and post-shipment monitoring. Data loggers such as tag sensors can be paste on the exterior of the box to measure surface temperature of the box.
- For products requiring different storage temperatures, other forms of packaging and refrigerants should be used.
- Risk assessment in identifying all the CCP in Cold Chain should be done.

Today's Problem - Recommendation

- At the hospital, the staff can adequately protect vaccines by doing the following:
    - Keep vaccines in appropriate vaccine refrigeration equipment.
    - Use a temperature monitoring device to ensure temperatures remain between +2 °C and +8 °C.
    - checking and recording vaccine temperatures twice daily; typically in the morning and at the end of the session or day
    - properly storing vaccines, diluents and water packs
    - handling preventative maintenance of the cold chain equipment.

Learning Outcomes

- Recognize the temperature, humidity, environmental sensitivity of pharmaceutical products, in particular, vaccines and antibiotics, which require stringent control in handling.
- Identify equipment used in pharmaceutical and bio-chem cold chain including packaging, temperature monitoring devices, and refrigerators.
- Identify the best industrial practices (cGMP/GDP) for the implementation of quality assurance system.