Safeguarding public health

Cold Chain Distribution For Pharmaceuticals

Regulations and Guidelines

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Temperature Controlled Distribution - The Issue

"Control of storage and transportation temperatures is essential in maintaining the quality of medicines and in helping to protect patients from sub-standard or ineffective medicines that may result from inadequate control"

[J Taylor, TCS&D, March 2002]

Why Has This Become an Issue?

- Increasing reliance on global distribution networks to satisfy the market
- Increasing number of temperature-sensitive products
- Increasing awareness by distributors that a lack of control of storage and transportation temperatures can have a major impact on product quality
- Increased surveillance by regulators

Good Distribution Practice

- Standards of good distribution practice (GDP) are applied to ensure that the high level of product quality achieved by observing good manufacturing practice is maintained throughout the distribution network

EC GDPs:
Storage Temperatures

- Products requiring controlled temperature storage should be identified on receipt and stored in accordance with written instructions
- Temperatures should be monitored and recorded daily. Records should be reviewed regularly
- Controlled temperature storage areas should be equipped with temperature recorders. Control should be adequate to maintain all parts of the area within the specified temperature range

EC GDPs:
Shipping Temperatures

- Medicines should be transported in such a way that they are secure and are not subjected to unacceptable degrees of heat and cold

- Medicinal products requiring controlled temperature storage should also be transported by appropriately specialised means

Why is MHRA Concerned about Temperature Control?

32% of all critical and major deficiencies recorded by MHRA's GDP inspectors during 2005/2006 related to the control and monitoring of storage and transportation temperatures.

Comparative data:

01/02	02/03	03/04	04/05	05/06
42%	52%	36%	43%	32%

Compliance Issues: Storage

- Temperature monitoring records
- Temperature mapping
- Alarm systems
- Response to out-of-specification (alarm) conditions
- Qualification/re-qualification
- Cleanliness
- Receipt of cold chain goods (time outside cold store)

Compliance issues: Transportation

- Monitoring devices and their locations
- Temperature monitoring records
- Shipping containers
- Controlled use of cooling elements
- Uncertain audit trail
- Temperature mapping of vehicles
- Contract transport, couriers and their audit

Calibration

- Manual and electronic recording devices used in critical areas 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 or corrections to be applied
- Alarms should be checked at least annually for correct functioning

Validation of Cold Chain Distribution

Each shipment between countries and within countries of large geographical area should be treated as unique in terms of the range of temperatures the goods may experience.

Risk Assessment: Matters to Consider

- Nature of the products (solids, semisolids, liquids)
- Labelled storage requirements and associated warnings
- Sensitivity of product to extremes of temperature
- Likely period of exposure to temperatures outside the labelled storage requirements
- Maximum and minimum temperatures that may be experienced by the product
- Exposure to fluctuating temperatures

Risk Assessment: Matters to Consider

- Number and nature of the stages in the chain
- Number of drop-off points in delivery chain
- MA holder's advice (in writing)
- Scale of the operation
- Support available (service providers)
- Knowledge and experience of potential contract acceptors

High Risk Products

- Products at risk from freezing:
  - vaccines, insulin, biotech products, blood products
  - those physically unstable, e.g. some emulsion systems

- Products at risk from elevated temperatures
  - those described above, and
  - those chemically unstable at elevated temperatures, e.g. chloramphenicol eye drops
  - some semi-solids, e.g. fatty-based suppositories

Discussions with Couriers

- Conditions under which materials should be transported
- Modes of transport
- Routes
- Transit times
- Shipping containers and labelling
- Couriers (and sub-contractors where appropriate)
- Special precautions (e.g. for hazardous materials)
- Communication
- Documentation
- Technical agreements and audit arrangements

Couriers' Responsibilities

- To know and comply with international requirements
- To know and comply with local requirements
- To know the nature of the goods and risks presented to and by them
- To be satisfied as to the capability of the couriers and their compliance with good practices
- To ensure that the terms and conditions of the technical agreements are complied with
- To know what to do in the event of excursions or non-compliance

Quality Management System

A quality management system is the organisational structure, responsibilities, procedures, processes, documentation and resources for implementing quality management

Quality Management Systems And Cold Chain Distribution

The system should ensure that:

- there is a programme of calibration of measuring devices
- storage facilities are monitored, qualified/re-qualified
- transport arrangements are validated and monitored
- there is a comprehensive staff training programme
- there is a periodic review of activities
- there is a process for implementing corrective and preventive actions and assessing their effectiveness

Temperate Chain Storage and Transportation

- Regulator's concerns are not restricted to cold chain storage and transportation:
- 17% of serious GDP deficiencies recorded by UK Inspectors during 2005/2006 related to temperature control and monitoring of the storage of medicines other than cold chain products

Inspection Finding: Temperate Storage

- “Temperatures are not monitored in the general storage areas. A thermometer taken from one of the offices indicated a temperature of 35°C on the mezzanine floor at the time of inspection”.

Inspection Finding: Cold Storage

- “An external monitoring station recorded an out of temperature limit alarm in a wholesale distributor’s 2-8°C cold room on a Saturday evening.
- The company’s Responsible Person was advised of this shortly afterwards, but no corrective action was taken until the following Monday, by which time the temperature in the cold room had risen to 25°C.
- No rationale was recorded for the decision by management not to take any action concerning the disposition of the stock in the cold room at the time of the incident”.

Inspection Finding:
Cold Chain Transportation

- “In general, cold chain products are not transported to customers under conditions that ensured that the labelled storage requirements of 2-8ºC are maintained.
- The company has no knowledge of the temperatures that goods in transit might experience during extremes of external temperature”.

What Happens When Things Go Wrong?

- Risk to patients
- Expensive recalls
- Loss of confidence in the company
- Regulatory action
  - suspension of manufacturing/distribution authorisation
  - compulsory variation of authorisation
  - revocation of authorisation
  - sanctions against the QP or RP

What Distributors Should Have In Place

- A comprehensive quality system
- A process for continual quality improvement
- A cold chain distribution strategy
- An ambient and cold chain distribution strategy
- A risk assessment programme

The Ultimate Objective

Organisations involved in the distribution of medicines should adopt a culture that focuses on:

- protecting the patient
- ensuring the quality of the products handled
- satisfying customer requirements

References

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* *www.pharmj.com*


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