Qualification and Monitoring of Temperature Controlled Storage Facilities

Pfizer Educational Programme

Chemical and Pharmaceutical Academy, Saint-Petersburg

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Agenda

Global Regulations

How temperature mapping and validation fit together

The main stages involved in temperature mapping studies

Permanent Monitoring Systems

Driving Cold Chain Visibility for Product Storage

A drug is adulterated if the facilities or controls used for its manufacture, processing, packing or holding do not conform to/are not operated or administered in conformity with current good manufacturing practice (cGMP)…

Adulteration under cGMP Requirements
(FFD & C Act [351(a)(2)(B)]

Reference: current Good Management Practices (cGMP) requirements from the US code (USC) Title 21, Chapter 9 - Federal Food and Drug Cosmetic Act (Subchapter V, Part A, 351 (a)(2)(B))

Regulatory Guidance

USP General Chapter <1079>

Qualification procedures on a regular basis should be independently conducted on equipment in cold stores to guarantee suitability and proper functioning…

The procedure should demonstrate the temperature profile for both air and product temperatures when empty as well as when loaded.

EU

CANADA

INDIA

Reference: 37(4) In-Process Revision: <1079> GOOD STORAGE AND DISTRIBUTION PRACTICES FOR DRUG PRODUCTS (USP35-NF30 2S), July 18, 2011

Irish Medicine Board

1.0	*Conditions within the distribution chain can vary markedly at different times of year. The environment also changes significantly according to the season and all of these variables have an influence on cold-chain distribution. Validation studies can provide an adequate level of assurance. Hence,* ***validation is required in order to assess the worst-case conditions.***
4.0	***Temperature mapping should be performed on all storage areas*** *to ensure that all locations are likely to remain within the specified temperature limits over the seasons of the year.*

Reference: Irish Medicines Board - Guide to Control and Monitoring of Storage and Transportation Temperature Conditions for Medicinal Products and Active Substances, IA-G0011-1, Version 1, October 2011

New EU GDP Guidelines

3.13	*…**adequate control** of the environment of medicinal products during storage*
3.16	*Storage areas should be **temperature mapped**…*
3.26	*Wholesale distributors should **identify what qualification and/or validation work is necessary to demonstrate control** of key aspects of their activities. The scope and extend of such validations should be determined by a documented risk assessment approach. Validation activities should be planned and documented. The plan should specify acceptance criteria.*

Reference: DRAFT Commission Guidelines on Good Distribution Practice of Medicinal Products for Human Use, Brussels, SANCO/C8/AM/an D(2010) 380358, open for public consultation until 31 December 2011

New EU GDP Guidelines

Premises and Equipment (Chapter 3):

- Storage areas should be temperature mapped
  - Under representative conditions
  - Initial mapping prior to use
  - Repeat based on risk assessment
- Location temperature monitors based on mapping
- Alarm system should be in place and tested periodically
- All equipment should be maintained to a suitable standard
- Equipment (e.g. temperature monitoring devices) should be calibrated regularly
- Records should be sustained

Reference: New European Commission "Guidelines on Good Distribution Practice of Medicinal Products for Human Use", March 2013

Regulatory Concern: Inadequate Storage Conditions

Looking at our recall data, I was surprised to see that one of the top issues is inadequate storage conditions [for drugs]

Motta, R., FDA Compliance Safety Officer
Division of Manufacturing and Product Quality Center for Drug Evaluation and Research

Reference: Motta, R., FDA, Compliance Safety Officer, Division of Manufacturing and Product Quality, Center for Drug Evaluation and Research – Washington Drug Letter - "FDA: Drug Storage Conditions Among Top Issues in Recalls" *– Vol. 42 No. 16 – April 19, 2010*

FDA Observations: Inspection of Warehouses

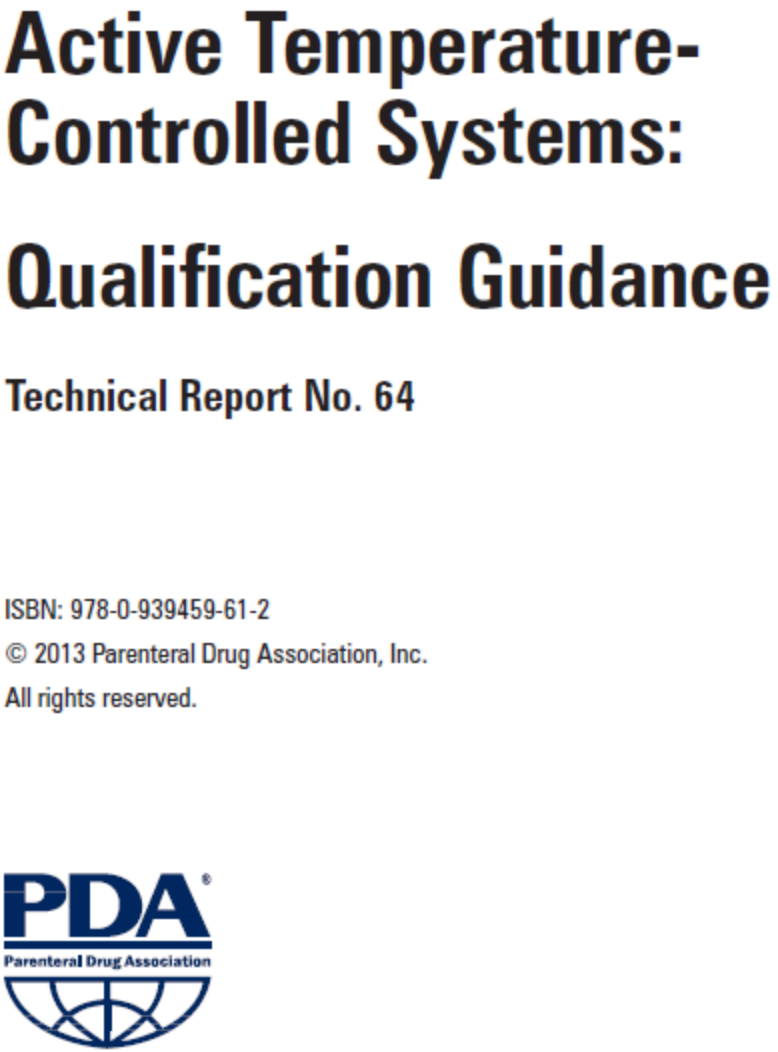
Findings:

- Over 50 inspections conducted
- 17 inspections resulted in an issuance of a FDA Form 483

34% of inspections resulted in an issuance of a FDA Form 483

Reference: Motta, R., FDA, Compliance Safety Officer, Division of Manufacturing and Product Quality, Center for Drug Evaluation and Research – PDA, PCCIG presentation "Cold Chain Management Requirements and Recommendations" – April 12, 2010

Industry Best Practice



TR 64: Active Temperature-Controlled Systems – Qualification Guidance

PDA Active Temperature-Controlled Systems: Qualification Guidance Technical Report Team

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Temperature Mapping

Temperature mapping is undertaken for the following reasons:

- Qualification exercise for a new facility
- First profiling of an existing facility
- 2 or 3 yearly periodic checks
- Significant change(s) made to a facility

Temperature Mapping/Validation [1]

Normally for new facilities:

- Temperature mapping is part of the validation life-cycle

Part of Operational Qualification (OQ):

- Mapping whilst empty:
  - Reasonable time period to demonstrate consistent performance:
    - For cold/freezer rooms – cover all compressor and defrost cycles
  - Alarm tests
    - Driving temperatures up and down to test limits (where possible)
    - May locally heat / cool sensors
    - May inject signals
  - Challenges such as observing spikes and recovery after door opening for Cold/Freezer stores
- Data may be used for ‘provisional’ instrument placement for monitoring system.

Temperature Mapping/Validation [2]

Part of Performance Qualification

- Loaded performance for warehouses cold stores and freezer rooms

Best approaches tend to be associated with new facilities and prospective studies

- Structured scientific approach (we'll look at this later)

Mapping studies of existing facilities can vary considerably in quality.

Examples of temperature mapping approaches [1]

A: 2-week extensive monitoring to determine hot and cold stops (e.g. during August - Europe)

- Fixing a limited number of routine monitoring probes at locations demonstrated to be at the extreme of range observed
- Assume monitoring probes give representative readings for whole working volume
- Review annual data from permanent routine probes

B: 2-week summer mapping & 2-week winter mapping

- Fixing a limited number of routine monitoring probes at locations demonstrated to be at the extreme of range observed after first 2-weeks
- Review routine monitoring locations after mapping repeated.

Examples of temperature mapping approaches [2]

C: Phased approach to mapping probe removal and routine monitoring probe installation

- Routine monitoring probes installed (from OQ data or initial investigation)
  - With flexibility to move them!
- Extensive mapping probes placed and left in place for a period of say 4 months
  - Routine monitoring probe location reviewed and moved if necessary
  - 50% [example] of mapping probes removed (based on data)
- Mapping continued for a further 8 months with phased removal of probes
  - Reduced to 25% at 8 months (based on data review)
  - All removed after 12 months
- PQ report written
  - Final routine monitoring probe location agreed

D: Full mapping for 12 months

- Extensive mapping for full 12 months
- Approach to routine monitoring probe location similar to example C.

Temperature Mapping Process

Approach will be the same, whether part of a qualification exercise or part of the first profiling of an existing facility

Require an approved protocol covering:

- Scope of mapping/qualification
- Test methods – objective methodology and acceptance criteria
  - Instrumentation requirements – instrument type
  - Instrumentation placement (maps)
    - Including rationale to support this!!
  - Sampling frequency
  - Acceptance criteria – upper + lower limits
- Data management/acceptance criteria
- Reporting.

Mapping Study – Key Steps

The key steps involved are:

- Step 1: Determine critical mapping points
- Step 2: Determine sample rate
- Step 3: Select instrumentation
- Step 4: Placement of data loggers (+ confirmation of placement)
- Step 5: Retrieval of data (+ confirmation of removal)
- Step 6: Report findings
- Step 7: Remedial action (if any)

Must integrate data logger maintenance and calibration.

Step 1 – Determine Critical Mapping Points [1]

Large open spaces generally involved:

- Present considerable challenge when working to maintain a consistent temperature or temperature/humidity level

Design and operating policy

- Strive to obtain and maintain even (homogeneous) compliant conditions throughout the anticipated storage area
  - Ensure spaces are de-stratified
  - Ensure control around set-point is adequate
  - Ensure systems can cope with weather extremes
  - Makes qualification easier with maximum chance of success
  - Maintains product quality and protects the patient

Older facilities and also some new facilities (although to a lesser extent) will have a level of problem areas.

Step 1 – Determine Critical Mapping Points [2]

Problem areas:

Areas close to ceilings or exterior walls:

- May stay warmer or cooler in response to temperatures outside

Temperature levels stratify:

- Warmer air rises and cooler air falls
- Temperatures will tend to be higher near heaters
- Undersized or improperly placed fans will be incapable of mixing the heated/cooled air effectively
- Racking, shelving and pallet storage areas may create “hot and cold spots” by obstructing air circulation

Doors that are left open will affect temperature

- Minimise openings wherever possible

Other heat sources, e.g. local air conditioning

Mezzanine floors.

Step 1 – Determine Critical Mapping Points [3]

Areas for consideration for monitoring locations (within load volume)

HVAC air supply and return

Evaporator outputs (cold/freezer stores)

Exits to unconditioned spaces (loading docs and staging areas)

Level of facility insulation

- Walls and roof – will they be hot or cold?

Outside:

- Measures seasonal challenge and correlate to internal temperatures

High, medium and low locations in the general storage area

Other areas that can hold product, e.g. goods out

- Operational control should minimise product hold in these areas!!

Dreaded roof windows (sky lights)

Step 1 – Determine Critical Mapping Points [4]

Location Spacing:

- Very much dependent on the design of the facility:
  - Poorly designed equipment / facilities
    - Locations will be more numerous and closer together (not evenly placed)
  - Modern well designed facilities
    - Less numerous points and more evenly spread

Determination of critical mapping points should include all potential problem spots in addition to the normal storage area

A rationale should be produced to support the location map

- Best practice is to cover this in the protocol.

Step 1 – Determine Critical Mapping Points [5]

Preparation of a sampling map:

- The map needs to clear and precise and allow 3-dimensional placement
  - This will require more than one 2 dimensional drawing (see later)
  - Possible use 3-D drawing
    - Difficult without the use of software
- Unique location number for each logger marked on map
  - Vital for reconciling data.

Step 2 – Determine Sample Frequency [1]

Determining sample frequency:

Needs to be sufficient to capture temperature trends:

- Too much data (too high a frequency):
  - Creates difficulties in processing and reviewing data
    - Can depend on type of system being used
  - Contributes no added value
- Too little data (too low a frequency)
  - Miss temperature trends and peaks and troughs

Generally the larger the space involved the slower the conditions change

- The lower the frequency of capture

Must consider the data collection aspects, e.g. logger memory capacity (becoming less of an issue these days).

Step 2 – Determine Sample Frequency [2]

Typical sampling frequencies:

- For large warehouse:
  - Every 30 to 60 minutes should be sufficient
- For cold/freezer stores:
  - Possibly every 10 minutes (depends on activity/risk):
    - Capture effects of door openings and evaporator control
    - May need to sample more frequently at OQ, e.g. door opening and recovery challenge – 30 seconds or 1 minute

61 locations, 30 minute sample interval for 12 months = 1,065,792 data points:

- Difficult to review without trending /graphical analysis
- Good data management is critical.

Step 3 – Select Instrumentation [1]

Criteria for selection:

Size, data capacity and sample rate

Ease of use

Monitoring range and accuracy

Wired connection or wireless

- Budget and/or facility interference may influence this
- If wired, how and when will you download data

Networking

- Ethernet connectivity:
  - Enables data logger interrogation/management from PC connected to Local Area Network:
    - View / download logged data
  - Modify logger settings

Battery Life

- Battery must last between mapping sessions.

Step 3 – Select Instrumentation [2]

Criteria for selection (continued):

Battery Life

- Battery must last between mapping sessions

Logger clock

- How will all loggers be synchronised
  - Could be linked to data download frequency
  - Could be automatic with wireless devices

Calibration

- Recommended calibration frequency?

Software:

- Ease of use
- Security features
- Data management.

Step 4 –Instrument Placement

Key considerations:

Wireless or not?

Need to account for the location of each logger/instrument

- Traceability of data to location

Logger labelled with location point - corresponding to map

Placement of all loggers documented

- Record sheet:
  - Protocol reference
  - Installer's name
  - Date and time installed
  - Identification of Logger
  - Verification of correct location in accordance with map
    - Sign / date
  - If data loggers are to be removed for data download/calibration record sheet should capture these events
    - You don't want deviations for data recorded in the engineering workshop!!!!

Step 5 – Retrieval of Data

Retrieval Methods - linked to type of device

Data transmitted continuously to central data receiver

- All data stored centrally – PC access to data server

Data downloaded locally using connection cables

- Must set times for down-loads (protocol)

Data loggers need to be gathered at end of mapping period

- Record date and time retrieved

PC Downloads

- Data saved to a secure backed-up server
- Process covered by a procedure (protocol/SOP)

May need to comply with electronic data guidelines/regulations

- 21 CFR Part 11 (Electronic Records, Electronic Signatures)
- EU Annex 11.

Step 6 – Reporting the Results [1]

Review of data required:

Many data points (over 1 million in example)

- Use of reviewing tools:
  - Device specific application
    - May produce trends and graphs for each or all loggers
  - Data export to Microsoft Excel
    - Charts produced
    - Conditional format function to highlight out of range data
    - Mean Kinetic Temperature calculation (if required)
    - Graphically show max, min and average
    - Very important that clocks are synchronised
    - Must keep original print-outs from individual loggers where applicable.

Step 6 – Reporting the Results [2]

The results will need to be incorporated into a report:

Part of an OQ or PQ report for a new facility

Generated against a mapping protocol

PQ may involve an interim report for each phase

Include summaries and results review

Compare data against acceptance criteria

- May include locations of routine probes

Deviations reported properly

Conclusion: Statement as to success of exercise

- All acceptance criteria met
- Stock can be stored (OQ) - Warehouse can be routinely used (PQ)

Detail remedial action (interim report).

Step 6 – Remedial Action

Outstanding deviations:

- Interim report normally generated when there are outstanding deviations (discrepancies)
  - Allows use of facility whilst deviations are resolved (providing no impact on product quality)
  - Don’t wait to the end of a study to deal with a known deviation

Could be a number of issues:

- Generally associated with out-of-specification temperatures
- Identify immediate corrective actions:
  - E.g. usage restrictions
- May have to detail longer term preventative actions:
  - Warehouse de-stratification
  - New heating/cooling systems.

Data Logger Maintenance and Calibration

Instruments can drift over time:

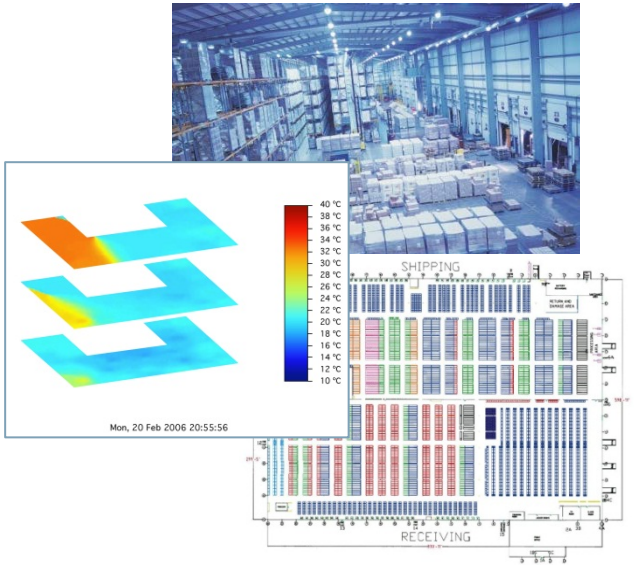
- Leading to inconsistencies in recorded data

It is recommended that each instrument be calibrated at least every 12 months

Calibration frequency must be considered in selection and use of loggers:

- e.g. Loggers may require calibration 8 months into a 12 month study:
  - How are you going to manage this?
  - Needs to be stated ‘upfront’ in the protocol otherwise you will be raising deviations
  - Procedure required for removal and reinstallation (within protocol).

Thermal Mapping Summary



Provide necessary documentation

- Document control of thermal environment during storage
- Identify thermal variances to support summer and winter profiles
- Identify and document potential problem areas
- Develop recommendations and strategies for reduction of thermal variability
- Meet regulatory requirements and guidelines
- Documentation to support audits and cGMP
- Identify and document optimal monitor placement
  - Develop “monitor placement protocol”

Reduce costs

- Avoid thermal excursions which can result in quarantine incidents or product loss

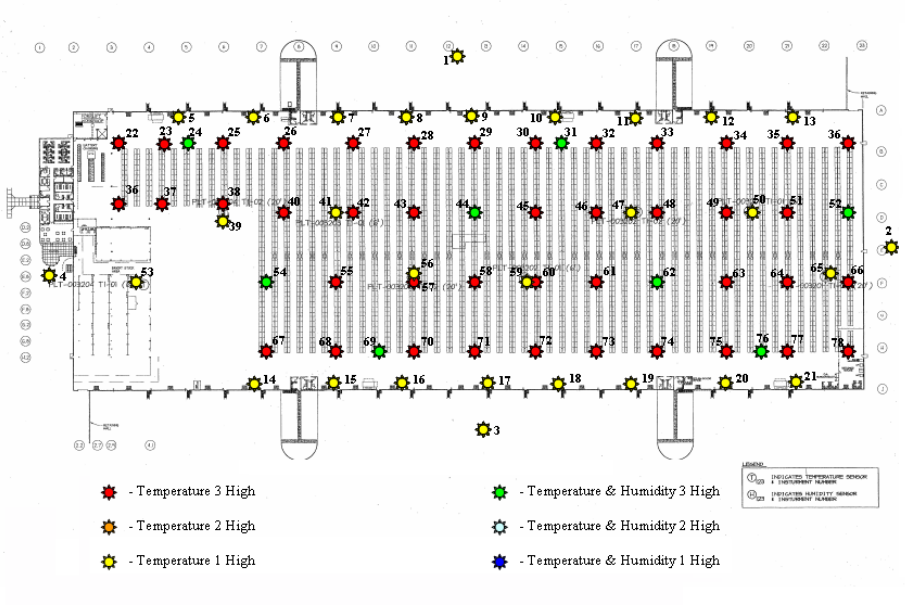
Protect brand equity

- Protect product quality and ensure product efficacy

Thermal Mapping Examples

Monitor Placement

- Based Placement Protocol
- Monitors are placed both horizontally and vertically for a comprehensive view of temperatures, airflow and the affects of contributors throughout the facility
- Balance between quantity of sensors and quality of outcome



Why is a Comprehensive Permanent Monitoring System Necessary?

Temperature-sensitive pharmaceuticals and biologics need to be maintained throughout supply chain to help ensure:

- Product quality
- Patient safety
- Global regulatory compliance

Many unforeseen and uncontrollable factors can cause products to go outside of acceptable temperature ranges

A comprehensive monitoring system can help to increase control and manage risk

Regulatory Guidance

USP General Chapter <1079>

When specific storage conditions are required, or in the absence of active or passive containers, ***environmental recorders or devices should be used*** *to confirm that an acceptable range has been properly maintained during each stage in the supply chain.*

EU

CANADA

INDIA

Reference: <1079> Good Storage and Distribution Practices for Drug Products (USP35-NF30 2S), US Pharmacopeia – Official December 1, 2012

Irish Medicine Board

3.1 Cold Storage	*The thermometer(s) should be placed within the load in a location which has been assessed to be the worst case and the temperature* ***should be measured continuously***
3.4 Freezers	*For small volume operations a* ***continuous temperature monitoring system must be employed***
	…should be monitored with an ***electronic continuous temperature-recording device*** *that measures load temperature in* ***one or more locations,*** *depending on the size of the unit*

Reference: Irish Medicines Board - Guide to Control and Monitoring of Storage and Transportation Temperature Conditions for Medicinal Products and Active Substances, IA-G0011-1, Version 1, October 2011

EU GDP Guidelines

3.2.1	Suitable equipment and procedures should be in place to check the environment… An initial temperature mapping exercise should be carried out on the storage area…
3.3	Equipment…should be calibrated… Appropriate alarm systems should be in place… Adequate records of repair, maintenance and calibration…

Reference: "Guidelines of 7 March 2013 on Good Distribution Practice of Medicinal Products for Human Use." Official Journal of the European Union C.68 (2013): 1-14. Print.

Facility Monitoring Goals

Operational Efficiency

- Avoid manual data collection
- View data from anywhere via standard web browser

Compliance and Control

- Audit log of system activities
- Qualified installation services (IQ, OQ, PQ)
- Annual service/replacement plan options available
- Built to comply with 21 CFR Part 11

Increased Visibility

- Sensors monitor temperature, humidity and other conditions
- Real-time and historical data access via a standard web browser
- Automated reports
- Alarming / alerting on sensor and system-level events

Thank You

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