Preparing your Supply for the Regulatory Provisions Outlined in Health Canada Guide-0069 from Frozen to CRT

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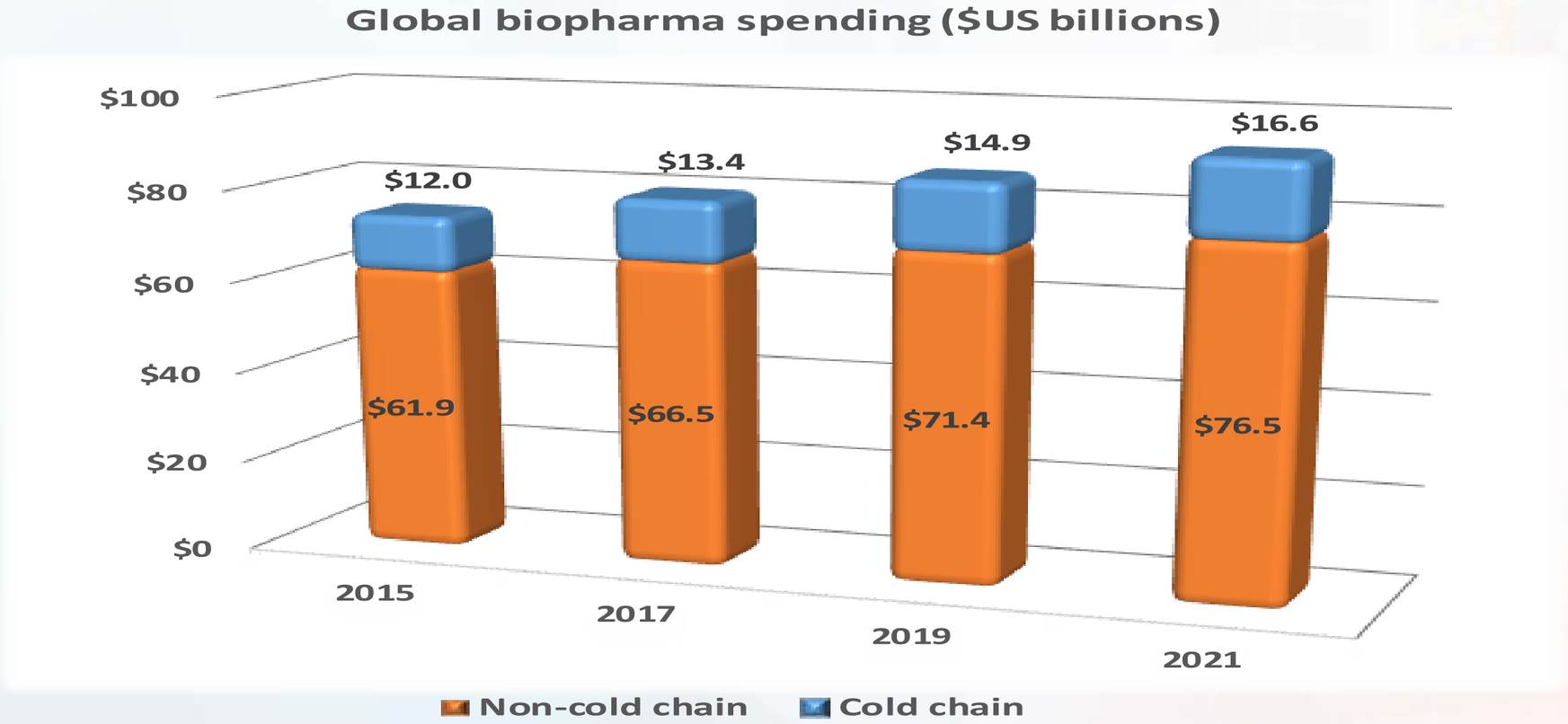
Pharmaceutical cold chain logistics is a $13.4-billion global industry



Cold chain logistics cost represents 16.7% of overall pharma logistics spend in 2017

Source: Posted in Clinical Operations, Cold Chain Focus, Supply Chain/Logistics | Tagged MAY/JUNE 2017

History of GUI-0069

- Initially published in 2005
  - Extensive review of all Worldwide Published documents concerning process for temperature control

- WHO, MHRA, FDA, IATA, ICAO, etc.
- USP–Pharmacopoeia, ICH Guidelines
- Scientific Articles

Question:

To what extend do we want the Health Canada Guideline to go?

Link to GUI-0069:
https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/good-manufacturing-practices/guidance-documents/guidelines-temperature-control-drug-products-storage-transportation-0069.html

Health Canada GUI-0069 Version 2
Food and Drug Regulations

- *Section C.02.010*

… the raw material has not been transported or stored under conditions that may affect its compliance with the specifications for that raw material.

- *Section C.02.011*

… Critical materials should be transported in a manner that does not adversely affect their quality.

…. Procedures are in place to ensure that media are transported under conditions that minimize the loss of moisture and control the temperature.

- Section *C.02.017*

…the packaging material has not been transported or stored under conditions that may affect its compliance with the specifications for that packaging material.

Health Canada GUI-0069 Version 2 (cont'd)
Food and Drug Regulations

- *Section C.02.019*

… the drug has not been transported or stored under conditions that may affect its compliance with the specifications for that drug.

- *Interpretation:*

Evidence should be available to demonstrate that each lot or batch received has been transported and stored in a manner that maintains the quality of the API. Further requirements are described in GUI-0069.

GUI-0069 Version 2
Scope

- All persons and companies involved in storage and transportation of drug products.
- Health Canada's jurisdiction (Fabricator [Manufacturer]/ Packagers / Testers / Importers / Distributors / Wholesalers)
- Written agreements between regulated parties and transportation providers
- Human, veterinary, clinical trial products and samples*

* Including Sales Representatives Samples

GUI-0069 Version 2
Warehousing and Storage

- Storage conditions (temperature, humidity, light, etc.)
- Temperature monitoring – sensors located at worst case scenarios of Refrigerators and Freezers, and must be calibrated
  - Equipped with alarms, well maintained, free from excessive frost buildup, be equipped with a backup power source, etc.
- Procedure of action in the case of temperature excursion from the set parameters
- Training of personnel

GUI-0069 Version 2
Product Transportation and Products in Transit

- Flexibility for shipping outside of label conditions for brief periods (stability and scientific justification needed)
- Transport process and containers should be designed to prevent damage and maintain quality of drug
- Shipping procedures should be established and qualified
- Controlled storage conditions during transit (environmental controls must be in place) (i.e. temperature, relative humidity, light, etc.)

GUI-0069 Version 2

Product Transportation and Products in Transit

- Packaging configuration which provides the primary means of environmental control should evidence that product remains within range
- Refrigerated vehicles and containers should be mapped and monitored if primary means of environmental control
  - Not necessary if qualified container, etc.
- Temperature / humidity monitoring devices calibrated at predetermined intervals
- Transportation practices by carriers, including any storage and/or transportation activities performed by sub-contractors, should be periodically verified by reviewing documentation

GUI-0069 Version 2

Trust and Moving Beyond Service to Success

- Trust Level One
  - Contractual and Service
    - Boundary time beyond trust for standard performance
    - Exchanged data transactions
- Trust Level Two
  - Competence and Satisfaction
    - Reliable trust for satisfactory performance
    - Some information sharing and cooperation
- Trust Level Three
  - Commitment and Success
    - Goodwill open ended trust giving beyond expectations success
    - Cognitive connected decision making

Source: After Dr. Mari Sako
SAPICS 2007, The Relationship Driven Supply Chain: from Service to Success, Stuart Emmett

GUI-0069 Version 2

Product Transportation and Products in Transit

Loading activities should be done in a manner that preserves the quality of the drugs

GUI-0069 Version 2

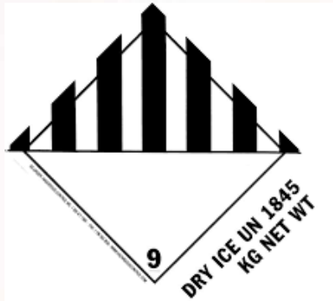
Product Transportation and Products in Transit

Did you plan for the unforeseen…

Shipping activities should be done in a manner that preserves the Quality of the product

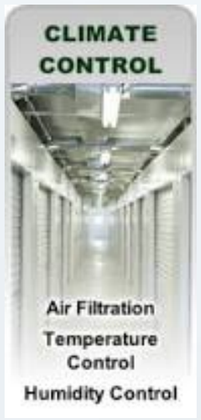
GUI-0069 Version 2
Containers and Container Labelling

- Controlled transport / storage conditions / warning statements should be clearly stated on label
- Shipping containers should be qualified
- Warm/cold packs
- Dry ice (Transportation of Dangerous Goods Act)
- Temperature monitoring devices and product disposition after an excursion



GUI-0069 Version 2
Receiving

- Receiving bays should protect deliveries from inclement weather and be separate from storage area
- Temperature sensitive drugs should be examined upon reception and results recorded
- Products should be promptly transferred to environmentally controlled storage area
- Controlled substances and narcotics



GUI-0069 Version 2
Documentation

- Written agreement between regulated party and carriers
- Maintain transportation records of inbound and outbound shipments*
- Records of investigations and actions taken after excursions*
- Temperature monitoring data and alarm records (includes maintenance and calibration records for monitoring equipment) should be maintained

*Records to be kept for a period of one year after expiration date of the product

"Eighty-five percent of the reasons for failure are deficiencies in the systems and process rather than the employee..."

W. Edwards Deming

7 Most Common Compliance Issues

- Temperature monitoring
- Temperature mapping in warehouses/storage areas
- Quality agreements
- Training of personnel
- Improper temperature range for selected device
- No assurance of product quality
- Procedures lacking significant elements

Health Canada

Sample Observations

* Information extracted from Health Canada presentation on Gui-0069 Ver2

Sample Observations

Risk: 2 - Major

Quality control department - C.02.015

- Evaluation of the actual transportation conditions considering seasonal variations had not been performed to ensure that products were maintained according to their labelled storage conditions. Additionally, the estimated maximum length of time required for transportation of the drugs, including any in transit storage had not been evaluated.

- The written quality agreements describing the respective responsibilities of the parties involved in the maintenance of the chain storage, transportation conditions, returned products, recalls, etc. between the company and the wholesalers were not all available.

* Information extracted from Health Canada presentation on Gui-0069 Ver2

Sample Observations
Risk : 3 - Minor

Quality control department - C.02.015

The shipping of finished product did not include a requirement to ship temperature sensitive products at labelled conditions. (E.g. Heated service in winter months if product susceptible to freezing)

There was no evidence that responsibilities for ensuring acceptable transport conditions would be included in quality contractual agreements.

* Information extracted from Health Canada presentation on Gui-0069 Ver2

Sample Observations
Risk : 3 - Minor

Quality control department - C.02.015

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* Information extracted from Health Canada presentation on Gui-0069 Ver2

"IF YOU THINK OF STANDARDIZATION AS THE BEST THAT YOU KNOW TODAY, BUT WHICH IS TO BE IMPROVED TOMORROW; YOU GET SOMEWHERE."

HENRY FORD, FOUNDER FORD MOTOR COMPANY

FDA 483 CITATIONS

- Products were not held at required temperatures during shipment.
- Specifically, the firm has no written procedure for: Drug Product Storage
- Specifically, there is no data to support the shipment of product X from the firm's contract cell bank to their contract manufacturer.
- The firm failed to hold the bulk drug product at the intended storage condition, specifically lot XXXX was kept at ambient conditions for 3-4 days prior to shipment

Excursion Events from the "Field"

Examples

- Product left in the mail box over the weekend…
- Forgot to put the product back in the refrigerator …
- Left the product in the car…

Excursion handling process

- Process to evaluate external excursions should be defined
- Available stability data used along with other information gathered to assess impact on product quality

Source: Robert H. Seevers, Ph. D., Eli Lilly and Company

Medicines & Healthcare products Regulatory Agency (MHRA) GDP Inspection Deficiency Data for 2016 published in November 2017

Top cited major GDP deficiency groups were:

- Quality Systems
- Transportation
- Responsible person
- Supplier Qualification
- Equipment
- Documentation
- Temperature Control
- Storage
- Customer Qualification

Brown, P., Madigan, T., and Ault M.: MHRA GDP Inspection Deficiency Data 2016. Published November 2017, https://www.gov.uk/government/uploads/system/uploads/attachment data/file/667494/GDP 2016 Deficiency data.pdf.

Lesson learned from Continued GDP inspections in the Netherlands based on the new EU GDP Guidelines

The results of the 35 inspections in 2016 showed 56 major findings:

- Temperature management in storage areas (12): temperature mapping and follow-up on alarms, lack of temperature control
- Quality management issues (10)
- Risk management (6)
- Management review (3)
- SOP's / CAPA's (3)
- Transportation issues (10): qualification and lack of temperature control
- Responsible Person (7)
- Qualification of suppliers and customers (5).

Bruinink, R., and Bishara, R. H.: Lessons Learned from Continued GDP Inspections in the Netherlands Based on the New EU GDP Guidelines. Journal Pharmaceutical Outsourcing, Volume 19, Issue 2, March / April 2018, pp. 16 - 17.

TYPES OF STABILITY STUDIES

- Accelerated ….. Stability indicating test
- Long Term ….. Shelf life and Expiry Dating
- One Lot per Batch per Year ….. Consistent and Maintained GMP
- Distribution ….. Freeze / Thaw, and Temperature Cycling Studies
- Dynamic ….. Shake / Vibration, Drop, pressure, heat, humidity

Non-Temperature Transportation Hazards

- Shock / Drop
- Vibration
  - ASTM 4169 and ISTA 3A
- Air Pressure
  - Surface Shipments
  - Air Shipments
- Humidity

Stability Budget

- A stability budget considers the results of long term, accelerated, freeze/thaw, and temperature cycling studies to determine the amount of time out of storage that a drug substance may experience without any significant risk to its quality.

References

- PDA Technical Report No. 53 – Guidance for Industry: Stability Testing to Support distribution of New Drug Products, 2011
- Van Asselt, E. J. and Bishara, R. H.: Establishing and Managing the Drug Product Stability Budget. Journal of Pharmaceutical Outsourcing, Volume 16, Issue 4, July / August, 2015, PP. 20 – 27.

Temperature Mapping

- Facility
- Equipment
  - Container
  - Vehicle and Trailer
- Protocol
  - -Rational for
  - -Number of probes or loggers
  - -Location of Probes or loggers
- - Minimum and Maximum load
- - Hot and Cold profile
- - Internal and External temperatures
- - Data collection and analysis
- - High risk areas

Temperature Mapping Factors

- (1) Size of space
- (2) Location of HVAC
- (3) Sun facing walls
- (4) Low ceiling or roofs
- (5) Geographic location of the area being mapped
- (6) Airflow inside the storage location
- (7) Temperature variability outside the storage location
- (8) Workflow variation and movement of equipment (weekday vs weekend)

Temperature Mapping Factors (continued)

- (9) Loading and storage patterns of product
- (10) Equipment capabilities (defrost and cycle modes)
- (11) Loading and unloading procedures of containers and vehicles
- (12) Route specific operation of the temperature control equipment
- (13) Seasonal effects encountered on expected routes
- (14) Loading Patterns
- (15) Transport Durations
- (16) SOPs

Guidelines for Temperature Control of Drug Products during Storage and Transportation (GUI-0069)

3.0 Interpretation

- 3.1 Warehousing and Storage
- 3.2 Product Transportation and Products in Transit
- 3.3 Containers and Container Labelling
- 3.4 Receiving
- 3.5 Documentation

STIMULI TO THE REVISION PROCESS
The Use of Mean Kinetic Temperature to Aid Evaluation of Temperature Excursions: Proper and Improper Application

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PF 44(4)

MKT Stimuli Article-PF44(4)

- The *Stimuli* article describes the use of mean kinetic temperature (MKT) to evaluate temperature excursions for shipments of controlled room temperature (CRT) and controlled cold temperature (CCT) pharmaceutical products.

- Correct and incorrect uses of MKT are described and supported by examples from actual events.

- The authors propose:
  - Using 30 days to calculate MKT for CRT products and
  - Using 24 h for CCT products, including excursion time.

Risk Valuation and Mitigation

Pharmacopeial Forum 44(4) In-Process Revision: <1079> GOOD STORAGE AND DISTRIBUTION PRACTICES FOR DRUG PRODUCTS

- 1. INTRODUCTION
- 2. SCOPE
- 3. RISK-BASED APPROACH TO THE STORAGE AND TRANSPORTATION OF FINISHED DRUG PRODUCTS
- 4. RISK MITIGATION CATEGORIES AS QMS ELEMENTS
- 4.1Documentation and Procedures
- 4.2 Training
- 4.3 Resources for Storage, Transportation, and Personnel
- 4.4 Qualification and Validation

<1079> References

- Seevers RH, Hofer J, Harber P, Ulrich DA, and Bishara R. The use of mean kinetic temperature (MKT) in the handling, storage and distribution of temperature sensitive pharmaceuticals. Pharmaceutical Outsourcing. May/June 2009;12–17.
- Andersen C, Seevers R, and Hunt D. The use of mean kinetic temperature to aid evaluation of temperature excursions: proper and improper application. Pharm Forum. 2018;44(4).

Comment deadline: September 30, 2018

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Key Takeaways

- (1) Keep up with the regulations and pharmacopeia standards
- (2) Learn from domestic and global inspections
- (3) Implement risk analysis and mitigation

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