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Health Products and Food Branch Inspectorate

Guidelines for Temperature Control of Drug Products during Storage and Transportation

GUI-0069

Supersedes:
October 17, 2005

Date Issued:
January 28, 2011

Date of Implementation:
April 28, 2011

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1.0 Introduction

Distribution and wholesaling form part of the supply chain of drug products. Drug products must be transported, handled and stored in a manner that mitigates the risk of exposure to temperatures outside labelled storage conditions; potentially impacting the safety, quality and effectiveness of the drug product. Section 11 of the *Food and Drugs Act (*http://laws-lois.justice.gc.ca/eng/F-27/index.html*)*, read together with the definition "unsanitary conditions" in Section 2 of the *Food and Drugs Act*, prohibits any person from:

> "*...packag[ing] or stor[ing] for sale any drug under ...such conditions or circumstances as might ....render [a drug] injurious to health*".

Fabricators, packagers/labellers, distributors, importers and wholesalers are additionally responsible for the appropriate handling, storage and distribution of drugs according to C.02.015 of the *Food and Drug Regulations* (http://laws-lois.justice.gc.ca/eng/C.R.C.-c.870/index.html). These requirements are in place to maintain the safety, quality and efficacy of the drugs. Every activity in the distribution of drugs should be carried out according to requirements of the *Food and Drugs Act*, the principles of Good Manufacturing Practices (GMP), as well as appropriate storage and transportation practices.

Environmental controls play a key role in maintaining drug safety, quality and efficacy. Temperature is one of the most important parameters to control. Drugs must be stored, and transported according to predetermined conditions (for example, temperature, etc.) as supported by stability data. Temperature excursions outside of their respective labelled storage conditions, for brief periods, may be acceptable provided stability data and scientific/technical justification exist demonstrating that product quality is not affected.

This guidance is not intended to cover every conceivable case. Alternative means of complying with the intent will be considered with appropriate scientific justification. Different approaches may be called for as new technologies emerge. This document builds on other pre-existing international guidance (see List of References).

2.0 Scope

These guidelines are intended to be applicable to all persons and companies involved in the storage and transportation of drug products. All persons and companies including fabricators, packagers/labellers, testers distributors, importers, and wholesalers have the responsibility for ensuring that appropriate storage and transportation conditions are maintained from the point of manufacturing up to the delivery of the drug products to the final distribution point. The maintenance of the chain of storage and transportation conditions should be supported by written agreements among the distributor, the importer, the wholesaler, and the transportation provider in order to preserve drug safety, quality and efficacy. The responsibility of each party, is to ensure that the required storage and transportation conditions are met through their respective GMP activities.

These guidelines apply equally to drugs for human and veterinary use and to clinical trial drugs for human use as required under C.05.010*(j)* and to samples that are distributed to professionals as per Section 14 of the *Food and Drugs Act*.

In cases where the requirements for blood and blood components for transfusion differ from what appears in Health Canada's guidance document entitled "Good Manufacturing Practices for Schedule D Drugs, Part 2,

Human Blood and Blood Components "
(http://www.hc-sc.gc.ca/dhp-mps/compli-conform/info-prod/don/sched_d_part2-annexe_d_part2_tc-tm-eng.php), the latter will take precedence. For requirements regarding cells, tissues and organs (CTO), please refer to Health Canada's guidance document entitled "Guidance Document for Cell, Tissue and Organ Establishments - Safety of Human Cells, Tissues and Organs for Transplantation"
(http://www.hc-sc.gc.ca/dhp-mps/brgtherap/reg-init/cell/cto_gd_ld-eng.php). Semen is excluded from the scope of this guide.

3.0 Interpretation

3.1 Warehousing and Storage

1. Storage conditions should be defined and described on the label of the product. All drugs should be stored according to the conditions described on the label. When specified on the label, controls for humidity, light, etc., should be in place. Storage areas should be designed or adapted to ensure good storage conditions. In particular, they should be clean, dry, have adequate circulation and maintained within acceptable temperature limits. To reduce human error, general storage areas are well lit.

2. The label should specify any special storage conditions required for the product. Adherence to these conditions should be checked, monitored and recorded. Temperatures should be controlled and monitored using calibrated monitoring devices and records of temperature and alarms, where applicable, should be maintained. Monitoring of storage facilities is conducted at points representing the worst case scenarios of the temperature range based on temperature mapping.

3. Refrigerators and freezers used to store drugs should:
   - be qualified (please refer to "Validation Guidelines for Pharmaceutical Dosage Forms - GUI-0029)"
     (http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/validation/gui_29-eng.php)
   - be well maintained,
   - be equipped with alarms,
   - be free from excessive frost buildup,
   - when combined, be a two door unit with separate freezer compartment and door,
   - allow for adequate air distribution and orderly storage within the chamber. Storage practices and loading configurations should not lead to the obstruction of air distribution,
   - have sensors for continuous monitoring and alarms located at the points representing the temperature worst case scenarios,
   - be calibrated as required by the calibration program,
   - be equipped with a backup power source or have alternate storage available in the event of a power failure for critical refrigeration equipment, including both walk-in and stand alone refrigerators/freezers or warehouses.
   - be of commercial grade and not be of household type, unless they incorporate the above controls. The use of household type refrigerators and freezers is discouraged.

4. Written procedures should be available describing the actions to be taken in the event of temperature excursions outside the labelled storage conditions. All excursions outside the labelled storage conditions must be appropriately investigated and the disposition of the stock in question must be evidence-based (for example, stability data and technical justification).

5. Appropriate training, as determined by the company, should be provided for personnel involved in warehousing and storage to ensure appropriate handling of temperature sensitive material. Records of this training should be maintained.

3.2 Product Transportation and Products in Transit

1. Drug products must be transported in a manner that ensures the products will be maintained within an acceptable temperature range as defined in the approved labelling and supported by stability data. Temperature excursions outside of their respective labelled storage conditions, for brief periods, may be acceptable provided stability data and scientific/technical justification exist demonstrating that product quality is not affected.

2. The transport process and containers should be designed to prevent damage and maintain the integrity and quality of the drug products. For example, transport conditions for ampoules should limit their exposure to physical stress to avoid the development of hairline cracks.

3. Written procedures for the shipping of drug products should be established. Such procedures should take into account the nature of the drug products, local conditions, modes of transport and any seasonal variations experienced, as well as describe any special handling precautions. These procedures should be qualified to ensure that appropriate conditions are maintained under probable extremes of ambient temperature and should also account for possible unforeseen delays which may occur in shipping/transportation (for example, delays at the border).

4. Where controlled storage conditions (for example, temperature, relative humidity, light, etc.) are required during transit, the necessary environmental controls must be in place.

5. Within a transportation container, the packaging configuration, which provides the primary means of environmental control for the drug product, should ensure that the drug product remains within the acceptable temperature range.

6. Refrigerated vehicles/transportation containers should be mapped and monitored, if they provide the primary means for environmental control. However, this may not be necessary if a qualified insulated container/package, or an appropriate temperature monitoring device on the package or selected packages, or gel packs or similar approved means, or lane profile data are used as the primary means of environmental control.

7. Temperature and humidity monitoring devices, such as data loggers, should be calibrated at predetermined intervals. Single use monitoring devices should be qualified (for example, verification of performance for indicator strips or freeze indicator units).

8. Transportation practices by carriers, including any storage and/or transportation activities performed by sub-contractors, should be verified by reviewing documentation. A record of the review should be kept and any discrepancies should have a follow up.

9. Vehicles and equipment used to distribute, store, or handle drugs should be suitable for their use and appropriately protective of the products to prevent exposure to conditions that could affect their stability and packaging integrity, as well as prevent contamination of any kind.

10. Loading activities (loading and unloading) should be done in a manner that preserves the quality of the drugs.

3.3 Containers and Container Labelling

1. Any controlled transport and/or storage conditions as well as warning statements (for example, "Time and Temperature Sensitive", "Do Not Freeze") should be clearly stated on the label applied to shipping containers. This label should be securely affixed and indelible. The label and shipping documents should clearly state that these products should be transferred without delay to the specified storage temperature upon receipt.

2. Shipping containers should be qualified to meet the expected extremes of ambient temperature within the distribution environment, if they provide the primary means of environmental control for the drug product.

3. Selection of a shipping container and/or box should be based on:
   - the storage and transportation requirements of the drugs,
   - the space required for the volume of drugs to be transported,
   - the anticipated extremes of ambient temperature,
   - the estimated maximum length of time required for transportation of the drugs, including any in transit storage.

4. When **warm/cold packs** are placed in containers used to transport drugs:
   - the type, size and number of packs should correspond to the shipping duration and temperature needed,
   - the location of the packs should ensure that the entire shipment of the product is maintained within the labelled storage conditions,
   - adequate barrier materials should be used to prevent contact between the packs and the products, if the packs are at a temperature outside the range acceptable for product storage.

5. The use of dry ice in the transportation of drugs must not adversely affect the drug product or the primary package and must be handled in accordance with the *Transportation of Dangerous Goods Act*. (http://laws-lois.justice.gc.ca/eng/T-19.01/index.html)

6. Temperature monitoring devices or temperature indicators should be used when appropriate. If temperature excursions outside predetermined temperature conditions, as per the labelled

storage conditions occur, these excursions must be assessed and documented to determine product disposition. Corrective action should be implemented where necessary and documented. Clear directions should be provided to the recipient for the evaluation of monitoring devices/indicators and disposition of the products.

3.4 Receiving

1. Receiving bays should protect deliveries from inclement weather during unloading. The reception area should be separate from storage area. Deliveries should be examined at receipt in order to check that containers are not damaged and that the consignment corresponds to the order.

2. Where controlled conditions (for example, temperature, relative humidity, light, etc.) are required during transit, the recipient should examine the shipment upon reception, following written procedures, to ensure the conditions have been met and record the results.

3. Products should be promptly transferred to the appropriate, environmentally controlled storage area.

4. Controlled drugs and substances subject to specific security requirements should be immediately identified and stored in accordance with written instructions and with relevant legislative requirements. Security on these products is monitored and maintained at the legally required level.

3.5 Documentation

1. When commercial carriers are used, all pertinent conditions should be specified in a written agreement between the distributor, importer or wholesaler, and the third-party. The contractors should comply with the written agreement.

2. Distributors, importers and wholesalers should maintain transportation records of inbound and outbound shipments, including monitoring records where applicable, for a period of one year after expiry date of the product.

3. Records of investigations and actions taken in the event of excursions outside predetermined temperature conditions, as per labelled storage conditions are kept for a minimum of one year after the expiration date of the product.

4. Recorded temperature monitoring data and alarm records should be available for review. The maintenance and calibration records of the equipment used for monitoring should be maintained.

Appendix A

Glossary of Terms

The following additional definitions supplement the definitions provided under the Glossary of Terms in the main "Good Manufacturing Practices Guidelines - 2009 Edition (GUI-0001)". (http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/docs/gui-0001-eng.php)

Carrier/ Transportation Provider - A person who is engaged in the transport of goods or passengers by any means of transport under the legislative authority of Parliament. (*Uniform Classification of Accounts and Related Railway Records*, April 1998, Canadian Transportation Agency). (http://www.otc-cta.gc.ca/doc.php?did=972&lang=eng)

Controlled Storage Conditions - Conditions that need to be maintained (for example, humidity, temperature, light) during the time the drug is transported and stored per the manufacturer's labelled storage conditions for the drug product.

Final Distribution Point - The final destination where the drug will be used or sold (for example, pharmacy, hospitals, clinics, retail stores, etc).

Lane/Route Profile - A lane/route profile is the temperature data collected on a product – outside of a temperature-protective shipping package – for a sample of the environmental conditions in the transportation routes that are used for shipping the product; such data can be used to qualify the shipping package and should be periodically monitored to ensure that changes have not occurred on the transport route that may affect the anticipated exposed temperatures. Such samples should be based on seasonal extremes.

Qualified shipping container/package - A package that can repeatedly demonstrate through documented testing, a high degree of assurance that the determined acceptance criteria are met and will maintain the quality of the drug product under such conditions.

Stability Data - Data from the accelerated storage condition stability study and, if appropriate, from the intermediate storage condition stability study can be used to evaluate the effect of short term excursions outside the labelled storage conditions (such as might occur during shipping).

Temperature excursion - A temperature excursion is a variance outside of the labelled storage conditions.

Appendix B

List of References

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