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To: Associations / Stakeholders

I am pleased to inform you that the final version of the guidance document entitled "Guidelines for Temperature Control of Drug Products during Storage and Transportation" is now available on Health Canada's Compliance and Enforcement website at:

http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/docs/index_e.html

This document was developed following the survey conducted in 2003 by Health Canada (HPFB Inspectorate) regarding transport and storage conditions of drug products. The results of this survey indicated a need for additional guidance to ensure that the requirement of the *Food and Drug Regulations* pertaining to storage and transport of drug products are met.

A draft document was posted for comments on the Inspectorate website in December 2004. The comments received have been reviewed by the Drug Good Manufacturing Practices (GMP) Committee and those that were accepted have been included in this new document.

Inquiries about this guidance document can be sent to the Manager, Drug GMP Inspection Unit, HPFB Inspectorate, by telephone at (613) 957-1492, by fax at (613) 957-6709 or by e-mail at GMP_questions_BPF@hc-sc.gc.ca.

Original signed by
Michelle Boudreau (for)

Jean Lambert
Director General

Health Canada
Health products and Food Branch

OUR MANDATE:

To promote good nutrition and informed use of drugs, food, medical devices and natural health products, and to maximize the safety and efficacy of drugs, food, natural health products, medical devices, biologics and related biotechnology products in the Canadian marketplace and health system.

Health Products and Food Branch Inspectorate

GUIDE-0069

Guidelines for Temperature Control of Drug Products during Storage and Transportation

Supersedes	Draft for comments
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Ce document est aussi disponible en français

Canada

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INTRODUCTION

Distribution and wholesaling form part of the supply chain of drug products. Drug products must be shipped and stored in a manner that does not risk exposure to temperatures outside of their *recommended storage conditions*[1]; potentially impacting the safety and effectiveness of the drug product. Section 11 of the *Food and Drugs Act*, 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*. These requirements are in place to maintain the quality 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), good storage and good distribution practices.

Environmental controls play a key role in maintaining drug quality. Temperature is one of the most important parameters to control. Drugs must be stored, handled and transported according to predetermined conditions (e.g. temperature, etc.) as supported by *stability data*[2]. Drugs that are particularly sensitive, such as drugs that must be kept refrigerated or frozen, must be handled with appropriate care.

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 is based on other pre-existing international guidance (see List of References).

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, distributors, importers, and wholesalers share 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*[3]. The maintenance of the chain of storage and transportation

[1] Predetermined temperature conditions as supported by stability data.

[2] Data from the accelerated storage condition and, if appropriate, from the intermediate storage condition can be used to evaluate the effect of short term excursions outside the label storage conditions (such as might occur during shipping).

[3] The final destination where the drug will be used or sold (e.g. pharmacy, hospitals, clinics, retail stores, etc).

conditions should be supported by written contractual agreements between the distributor, the importer, the wholesaler, and the transportation provider. The responsibility of each party, is to ensure that the required storage and transportation conditions are met through their respective GMP activities.

These guidelines not only apply to drugs for human and veterinary use but also 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 Drug Act*.

INTERPRETATION

1. WAREHOUSING AND STORAGE

1.1 All drugs should be stored according to conditions described on the label. When specified on the label, controls for humidity, light, etc. should be in place.

1.2 Temperatures should be controlled and monitored using calibrated monitoring devices and records of temperature and alarms, were applicable, should be maintained. Monitoring is conducted at points representing the extremes of the temperature range based on temperature mapping.

1.3 Refrigerators and freezers used to store drugs should:

- be well maintained,
- be equipped with alarms,
- be free from 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 extremes.

1.4 Written procedures should be available describing the actions to be taken in the event of temperature excursions outside the labeled storage conditions. All excursions outside the labeled storage conditions must be appropriately investigated and the disposition of the stock in question must be evidence-based.

2. PRODUCT TRANSPORTATION AND PRODUCTS IN TRANSIT

2.1 The transport process and containers should prevent damage and maintain the integrity and quality of the drug products. For example, ampoules exposed to physical stress could develop hairline cracks.

2.2 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 and any seasonal variations

experienced, and describe any special handling precautions. These procedures should be verified to ensure that appropriate conditions are maintained under worst case scenarios.

2.3 Where *controlled storage conditions*[4] (e.g. temperature, relative humidity, light, etc.) are required during transit, the *necessary controls*[5] must be in place.

2.4 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.

2.5 Refrigerated vehicles/transportation containers should be mapped and monitored, if they provide the primary means for environmental control. However, this is not necessary if a qualified insulated container is used as the primary means of environmental control.

2.6 Temperature and humidity monitoring devices should be calibrated at predetermined intervals. Single use monitoring devices should be qualified.

2.7 Transportation practices by *carriers*[6], including any storage and/or transportation activities performed by sub-contractors, should be periodically verified by reviewing documentation. A record of the review should be kept and any discrepancies should have a follow up.

3. CONTAINERS AND CONTAINER LABELLING

3.1 Any controlled transport and/or storage conditions as well as warning statements (e.g. “Perishable Drug Product”, “Do Not Freeze”) should be clearly stated on the label applied to shipping containers. This label should be securely affixed and indelible. The shipping documents should clearly state that these products must be transferred to the specified storage temperature immediately upon receipt.

3.2 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 amount of drugs to be transported,
- the anticipated external temperature extremes,
- the estimated maximum length of time required for transportation of the drugs, including any in transit storage.

[4] Conditions that need to be maintained (e.g. humidity, temperature, light) during the time the drug is transported and stored as per the manufacturer’s labelled instructions for the drug product.

[5] Procedures are followed and criteria are met.

[6] 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)

3.3 When warm/cold packs are placed in containers used to transport *temperature sensitive drugs*[7]:

- the type, size and number of packs should correspond to the shipping duration and temperature needed,
- the location of the packs should ensure the product is maintained within the recommended storage conditions,
- frozen packs should be conditioned prior to final packing by allowing them to "sweat",
- adequate barrier materials should be used to avoid direct contact of the packs with the products.

3.4 When dry ice is placed in containers used to transport temperature sensitive drugs, in addition to safety issues, it must be ensured that the dry ice or its vapours does not have an adverse effect on the drug product or its primary package.

3.5 Cold-chain monitors (CCM) or temperature indicators should be used when appropriate. If temperature excursions outside the labeled storage conditions occur, product disposition must be evaluated and documented. Corrective action should be implemented where necessary and documented. Clear directions should be provided to the recipient for the evaluation or disposition of CCM/indicators and products.

4. RECEIVING

4.1 Where controlled storage conditions (e.g. temperature, relative humidity, light, etc.) are required during transit, the recipient should examine the shipment upon reception following written procedures.

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

5. DOCUMENTATION

5.1 When commercial carriers are used, all pertinent conditions should be specified in a written contract between the distributor, importer or wholesaler, and the third-party. All contract acceptors should comply with the requirements in this guideline as applicable.

5.2 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.

5.3 Records of investigations and actions taken in the event of excursions outside the labeled storage conditions are kept for a minimum of one year after the expiration date of the product.

[7] A drug that can be altered with the exposure to temperatures that are not within the limits that have been demonstrated to be acceptable for the drug.

LIST OF REFERENCES

1. Good Distribution Practices (GDP) For Pharmaceutical Products, WHO- 2004, # QAS/04.068

2. Canada Communicable Disease Report, Vol.21-11, dated 15 June 1995

3. "Keep it Cool: the Vaccine Cold Chain; Guidelines for Immunization Providers on Maintaining the Cold Chain", 2nd. Edition, Commonwealth of Australia 2001

4. EU Guidelines on Good Distribution Practice of Medicinal Products for Human Use (94/ C 63/ 03)

5. ICH Q7A (18), Chapter 10, "storage and dispatch"

6. "Medicinal Cold Chain Guideline", PDA Draft document

7. "Good Storage and Shipping practices: Distribution and Shipment of Pharmacopoeial Articles" USP Draft <1079>

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