ADEQUACY OF THE COLD CHAIN

USED FOR THE STORAGE OF HEAT-SENSITIVE PHARMACEUTICALS

IN A DEPARTMENT OF ANAESTHESIOLOGY

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, in partial fulfilment of the requirements for the degree

of

Master of Medicine in the branch of Anaesthesiology

Johannesburg, 2019

DECLARATION

I, Graham Anthony Boy, declare that this research report is my own, unaided work. It is being submitted for the degree of Master of Medicine in the branch of Anaesthesiology at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

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ABSTRACT

Background

Anaesthesia frequently involves administration of refrigerated intravenous drugs to patients. Often overlooked, maintenance of the cold chain forms a key component of pharmacovigilance for anaesthetists. However the South African national Department of Health guidelines on: “Cold Chain and Immunisation Operations Manual”, does not detail specific requirements for medically validated cold boxes. Consequently the risk of iatrogenic harm to patients from heat-sensitive pharmaceuticals in inappropriately temperature regulated cold boxes exists.

Methods

The research design was that of a descriptive, prospective and contextual study. Part I study population comprised the ambient air temperatures of the refrigerator and cold boxes used for storage of heat-sensitive pharmaceuticals in theatre at CHBAH taken at one minute intervals over eight hours. Part II study population was newly purchased cold boxes and cold packs for the purpose of assessing individual cold box thermal performance over eight hours.

Results

In Part I, only a single cold box (polystyrene box number 19) was able to maintain the recommended temperature range of 2 − 8°C for the eight hour period (4.35%). The refrigerator temperature time plot showed a significant deviation of temperature at approximately 30 minutes.

In Part II, only fabric and polystyrene cold boxes with three cold packs in situ were able to maintain the recommended temperature of 2 − 8°C.

Conclusion

This study highlighted the failure of non-medically validated cold boxes to reliably maintain the temperature of heat-sensitive pharmaceuticals.

ACKNOWLEDGEMENTS

I would like to acknowledge and thank my supervisors Mrs J. Scribante, Mrs H. Perrie and Dr T. Kleyenstuber for their knowledgeable advice and guidance.

TABLE OF CONTENTS

FIGURES

TABLES

NOMENCLATURE AND ABBREVIATIONS

NOMENCLATURE

The following definitions will be used in this study.

Cold chain: a system consisting of people, equipment and heat-sensitive pharmaceuticals which ensure the temperature is maintained within a specified temperature range from the time of production through to the administration thereof. In this study the cold chain is from the refrigerator in the Department of Anaesthesiology to the administration of the medication from the cold boxes in theatre.

Cold life: the moment when the container lid is closed until the temperature of the warmest point in the vaccine storage compartment first reaches +10°C, at a constant ambient temperature of +43°C.

Mean kinetic temperature: the single calculated temperature, at which the total amount of degradation over a particular period, is equal to the sum of the individual degradations that would occur at various temperatures.

Cold box: for the purpose of this study, “cold box” refers to storage containers used in the theatres for the storage of heat-sensitive pharmaceuticals. The commercially available cold boxes used at CHBAH are either: fabric, polystyrene or hard plastic. These cold boxes do not conform to medically validated criteria for storage of heat-sensitive pharmaceuticals.

Cold pack: a water-pack frozen to a temperature between −5°C and −20°C before use.

Cool pack: a gel pack pre-cooled to a temperature between +2°C and +8°C before use.

Correctly packed cold box: refers to a cold box containing correctly prepared cold packs that are initially frozen at −5°C to −20°C, allowed to precipitate out of the freezer, wrapped in bubble wrap and subsequently placed into the cold box. Heat-sensitive pharmaceuticals

still in their secondary packaging are then placed on top of/next to the prepared cold packs with a data logger thermometer (DLT) placed in the central drug compartment. A further bubble wrapped cold pack should then be placed on top of the central drug compartment to seal it and the lid of the cold box closed.

Data logger thermometers (DLT): for the purpose of this study DLT refers to scientifically validated and calibrated thermometers used for continuous logging of temperatures. MAJORTECH® MT643 K-type temperature data loggers were used. These DLTs have a temperature range of −200°C to +1370°C with an accuracy of ±1°C.

Garage – this is term used to describe the area at CHBAH where the refrigerator containing cold/cool packs and heat-sensitive pharmaceuticals are kept.

Weekday – will be Monday to Friday from 08:00 to 16:00.

ABBREVIATIONS

CCT – controlled cold temperature

CHBAH – Chris Hani Baragwanath Academic Hospital

CRT – controlled room temperature

EMS – emergency medical services

EPI – injectable epinephrine

ICH – International Conference on Harmonisation

MKT – mean kinetic temperature

PDA – Parenteral Drug Association

USP – United States Pharmacopoeia

WHO – World Health Organisation

SECTION ONE - LITERATURE REVEIW

1.1 Introduction

This literature review will address aspects pertaining to pharmacovigilance, the cold chain as well as the impact of temperature excursions on heat-sensitive pharmaceuticals used in the practice of anaesthesia.

1.2 Pharmacovigilance

Anaesthesia frequently involves the administration of potent refrigerated drugs to patients with the ever-present potential for harm. Drug administration errors are common within health care systems and reported to be the seventh most common cause of death (1). These administration errors pertain not only to the wrong-drug-wrong-patient scenario, but to all facets related to the appropriate handling and storage of heat-sensitive pharmaceuticals. Pharmacovigilance which is defined as, “the science and activities concerned with the detection, assessment, understanding and prevention of adverse drug reactions to medicines” (2), therefore forms a critical component in the diminution of iatrogenic harm and the administration of safe pharmaceutical products.

A key facet of pharmacovigilance for heat-sensitive pharmaceuticals pertains to the cold chain and its maintenance. According to the South African national Department of Health Cold Chain and Immunisation Operations Manual of 2015, the cold chain is defined as “a system consisting of people, equipment and heat-sensitive pharmaceuticals such as vaccines, which ensures the correct quantity of potent vaccine/medicine reaches children, women or men who need it. The temperature of these items must be maintained within a specified temperature range from the time of production through to administration thereof” (3). It is a major concern of all regulatory authorities and manufacturers within the pharmaceutical industry to guarantee that drugs are delivered to patients without loss of therapeutic properties or the formation of potentially harmful degradation products (4). The United States of America Pharmacopeia’s (USP) Medmarx® medication-error reporting system has reported nearly 1000 incidences involving errors associated with refrigerated medications, many of which are attributable to inappropriate storage of medications (5). Within South

Africa, Kupper et al (6) has shown that the storage and presentation of drugs in theatres influences the likelihood of drug errors. It is common practice for the anaesthetic registrars of the University of the Witwatersrand (Wits) circuit to collect and store heat-sensitive pharmaceuticals in cold boxes for use within theatre prior to their administration. As such the potential for temperature excursions of heat-sensitive pharmaceutical products exists. Anaesthetists are therefore uniquely positioned as end users of refrigerated products and thus play a critical role in the maintenance of the cold chain and prevention of iatrogenic harm to patients.

1.3 Cold chain

Understanding the critical importance of maintaining the cold chain, international and national authorities have produced documentation on cold chain maintenance throughout the processes of manufacturing, transportation, storage and distribution. These include but are not limited to the following.

- World Health Organization (WHO):
    - Document QAS/04.068 on Good Distribution Practices “In order to maintain the original quality, every activity in the distribution of pharmaceutical products should be carried out according to the principals of Good Manufacturing Practice, Good Storage Practice and Good Distribution Practice ” (7).

- International Conference on Harmonization:
    - Q1A (R2) (8).

- Parenteral Drug Association:
    - Technical Report No. 39. Cold Chain Guidance for Medical Products: Maintaining the Quality of Temperature-Sensitive Medicinal Products Through the Transportation Environment, Revised 2007 (9).
    - Technical Report No. 46. 2009 Last Mile: Guidance for Good Distribution Practices for Pharmaceutical Products to End User (10).

- USP:
    - Chapter 795 Pharmaceutical Compounding – Nonsterile Preparations
    - Chapter 797 Pharmaceutical Compounding – Sterile Preparations
    - Chapter 1150 Pharmaceutical Stability
    - Chapter 1079 Good Storage and Shipping Practices
    - Chapter 1118 Monitoring Devices – Time, Temperature, Humidity
    - Chapter 1191 Stability Considerations in Dispensing Practice (11, 12).

- Department of Health Republic of South Africa Cold Chain and Immunisation Operations Manual of 2015:
    - Guidelines for Handling Temperature Sensitive Vaccines and Pharmaceuticals (3).

Failure to adhere to these documents could result in the administration of potentially compromised pharmaceutical products from various processes of degradation. The degradation experienced by pharmaceutical products is a complex and multifaceted process dependent on numerous factors including: physical and chemical properties of the ingredients, interaction between active and inactive ingredients, container closure system, and environmental conditions encountered as well as length of time between manufacture and product usage (13). It is temperature however that is deemed to be the single most critical factor involved in drug degradation. This is particularly so in the case of heat-sensitive pharmaceutical products in which the maintenance of a narrower temperature range of 2 − 8°C is critical to maintenance of product integrity.

Implicit to good manufacturing practice is for manufacturers to supply shelf life and expiration dates for every manufactured product. The difference between the two aforementioned can be gleaned from the respective definitions. Shelf life is defined as “the time during which the product if stored appropriately will retain fitness for use (>90% of label claim potency)” (11). Expiration date is defined as “the time up to which the preparation will remain stable when stored under recommended conditions, the date

beyond which it is predicted that the product may no longer retain fitness for use (14)", or " the date placed on the container/label of drug product designating time during which a batch of the product is expected to remain within the approved shelf life specification if stored under defined conditions and after which it may not be used" (8).

The consequences of a break in the cold chain are therefore reduced potency (shelf life), different compound formation within the drug product and potentially the generation of toxic substances (expiration date) (15). Determination of a products shelf life and expiration date is accomplished by pharmaceutical analysis in conjunction with accelerated and long-term stability testing studies. Table 1.1 is a list of recommended stability studies from ICH Q1A (8) and the WHO (7) for refrigerated products at 2 − 8°C.

Table 1.1 Stability studies employed for refrigerated products (2 − 8°C)

	Testing condition ICH Q1A (8)	Testing condition WHO Annex 5 (7)
Long-term stability study	5°C for 12 months	5°C for 12 months
Accelerated stability study	25°C/60% relative humidity for 6 months	None
Temperature excursion study	• −20°C for 2 days • 40°C/75% relative humidity for 2 days	None
Thermal cycling study	−20°C for 2 days followed by 25°C/60% relative humidity for 2 days Repeat for a total of 3 cycles	None

Accelerated stability testing, temperature excursion and thermal cycling studies (8), are of particular importance when considering the cold chain and the manner in which heat-sensitive pharmaceuticals are stored in cold boxes.

Key to understanding stability studies and the effects of temperature on heat-sensitive pharmaceuticals on shelf life is the concept of mean kinetic temperature (MKT) within a controlled cold temperature (CCT). The MKT is defined in the ICH Q1A document as (8): “a single derived temperature, that if maintained over a defined period of time, affords the same thermal challenge to a drug substance or drug product as would be experienced over a range of both higher and lower temperatures for an equivalent defined period. The mean kinetic temperature is higher than the arithmetic mean temperature and takes into account the Arrhenius equation.” (8). The MKT is therefore a weighted non-linear average that shows the effects of temperature variation over time and is established for a defined period using the Haynes equation as follows (16).

$$MKT = \frac{[\Delta H/R]}{-\ln[[e^{-\Delta H/RT1} + e^{-\Delta H/RT2} + \ldots + e^{-\Delta H/RTn}]/n]}$$

Where:

ΔH – Energy of activation (83.144 kJ/mol)

R – Universal gas constant (0.0083144 kJ/mol)

T_1 – arithmetic mean of highest and lowest temperatures recorded during the first time period in degrees Kelvin (K)

T_2 – arithmetic mean of highest and lowest temperatures recorded during the second time period in degrees Kelvin (K)

T^n – arithmetic mean of highest and lowest temperatures recorded during the nth time period in degrees Kelvin (K)

n – total number of temperatures recorded”

CCT is defined by the USP as: “the temperature maintained thermostatically between 2°C and 8°C. It allows for excursions in temperature between 0°C and 15°C that may be experienced during storage, shipping and distribution such that the allowable calculated MKT is not more than 8°C. Transient spikes up to 25°C may be permitted if the

manufacturer so instructs and provided that such spikes do not exceed 24 hours unless supported by stability data or the manufacturer instructs otherwise." (11) The USP proposed method of calculating MKT uses 52 weekly arithmetic means of the highest and lowest temperatures for calculating yearly MKT. (14)

The MKT then allows for determination of a degradation rate constant at the CCT which is defined as the single calculated temperature, at which the total amount of degradation over a particular period is equal to the sum of the individual degradations that would occur at various temperatures. It therefore represents the expected impact of temperature variations on the quality of the drug product as described by Grimm (17). There are however problems with potential conclusions drawn from the aforementioned.

At higher temperatures, even than those which may have been evaluated in accelerated stability tests, kinetics of degradation may change and other routes of degradation may become possible. The relationship between degradation rate and temperature may not always be linear or pseudolinear and therefore degradation reactions may not display zero or first order kinetics. Significantly, different rates of degradation at higher temperatures have been noted in various drugs (18). The value given for the activation energy of 83.144 kJ/mol in the Haynes equation is for covalent bonds and potentially lower activation energy may be required as with the case of hydrogen bonds seen in tertiary or quaternary protein molecules e.g. insulin (19). The selection of the size of the time increment to temperature excursions is also critical in evaluating the temperature history of a drug and the potential detrimental effect it may have to product quality. It has been shown by Seevers et al (19) that the calculated MKT over long periods is not sensitive to the impact of short temperature excursions and that these excursions could have significant impact on the resulting short term MKT. The author's recommendation is to compare the length of actual excursion approximating its magnitude with the calculated MKT against product stability data. This is due to long temperature histories potentially masking the effect of much shorter temperature excursions. At temperature excursions above that specified for the stability data of the product, significant risk may be present and the tolerance for short term exposure may vary widely (19).

Consideration should also be given to the effect of the thermal capacity of a product when exposed to temperature excursions and temperature spikes e.g. a 1ml ampoule will have a far greater sensitivity to temperature changes owing to its lower thermal capacity/mass than a similar 1l glass bottle of aqueous injectate. (14)

On the opposite end of the temperature spectrum, exposure to lower temperatures approaching 0°C may cause agglomeration of protein solutions or cause phase changes within drug products (19). There have been numerous case reports of frozen ampoules of both succinylcholine and thiopental encountered within the emergency setting of obstetric anaesthesia (20-22). Exposure below 0°C may also lead to damage of the container/closure system comprising packaging integrity i.e. hairline cracks in vials therefore compromising the sterility of pharmaceutical products prior to administration (23). The container closure system refers to the sum of packing components that contain and protect the dosage form or drug product and is divided into primary or secondary packaging. The primary packaging consists of the component in direct contact with the dosage form e.g. vials, bottles, syringes etc. Secondary packaging refers to those that are not in direct contact with the dosage form e.g. trays, cartons, overwraps etc. It is important to note that the entire closure system must be temperature controlled throughout the transportation and distribution processes. It is therefore crucial to maintain the integrity of the container closure system throughout the cold chain distribution process.

MKT is not recommended for the compensation of temperature excursions, especially in controlled cold temperature products and in areas where temperature is not well controlled (24). Temperature excursion as defined by the European Compliance Academy is “any deviation from the labelled storage condition of the product for any duration, whether during transportation or distribution” (25). It is therefore imperative that all temperature excursions be investigated and their impact on product integrity elucidated. Current manufacturer’s recommendations for the storage of commonly used heat-sensitive pharmaceuticals on Chris Hani Baragwanath Academic Hospital (CHBAH) Department of Anaesthesiology are listed in Table 1.2.

Table 1.2 Manufacturer recommendations for the storage of commonly used heat-sensitive pharmaceuticals at CHBAH

Brand name (Manufacturer)	Vial description	Minimum temperature (°C)	Maximum temperature(°C)	Duration of Storage at Room Temperature (RT)	Able to freeze	Protect from Light
Tracrium® (Aspen Global)	2.5ml 1%	2° C	8°C	14 days	No	Yes
Nimbex® GlaxoSmithKline	2.5ml 0.2%	2° C	8°C	21 days at RT 45 days at 23°C	No	Yes
Actrapid® Novo Nordisk	10ml vial 100IU/ml	2° C	8°C	Discard after 4 weeks at RT	No	Yes
Syntocinon® Novartis	1ml 10IU	2° C	8°C	Store below 25°C for 6 months, then discard	Not specified	Not specified
Esmeron® Schering-Plough	5ml 1%	2° C	8°C	Do not return to 2 − 8°C storage after it has been kept outside the refrigerator 8 − 30°C. Date of removal noted on the vial and product discarded if not used in 12 weeks	Not specified	Not specified
Suxamethonium Chloride	2ml 5%	2° C	8°C	Unstable after 14 days with cyclical cooling and heating 6 − 54°C every 12 hours	No	Exposure to light may change appearance and product attributes

There is a paucity of information and recommendations from manufacturers pertaining to the effects of temperature excursions, cyclical temperature changes and freeze-thawing of heat-sensitive pharmaceuticals. Pharmaceutical manufacturers are not required to report at what temperatures their products are stable at, but are rather required to manufacture products stable within environments dictated by their package labelling (26). This is in accordance with criteria stipulated by the USP. Of note,

laudanosine which is formed as a major product of metabolic degradation of atracurium and cisatracurium is a known epileptogenic substance. Its concentration increases with increasing time even if stored at the appropriate temperature (27, 28). Therefore, its storage necessitates strict adherence to the appropriately prescribed manufacturer storage conditions. All of the aforementioned aberrant storage conditions are possibilities given the manner in which heat-sensitive pharmaceuticals are stored within cold boxes.

1.4 Impact of temperature excursions on MKT

Studies within the emergency medical services pre-hospital environment have provided some insight into the aforementioned effects of the variable and often extreme effects of temperature excursions experienced by drug boxes and heat-sensitive pharmaceuticals contained within. A study conducted by Valenzuela et al (29) into the effect of extreme environmental temperatures on four standard paramedic drug boxes each containing identical sets of drugs showed internal temperatures of 26 − 38°C recorded within the drug boxes. The drug boxes internal temperatures closely reflected the external ambient temperatures experienced. This was further corroborated by DuBois (30) who found that temperatures inside drug boxes that were not actively cooled were as hot or hotter than the outside ambient air temperature (30). Valenzuela et al (29), subsequently showed via gas chromatography-mass spectrometry that isoproterenol parent compound degraded by 11% in a four week period and that the majority of medications showed little evidence of degradation (29). However these medications were intended for storage at CRT and not CCT and as such refrigerated products would have had a higher relative MKT and therefore would have experienced more deleterious effects.

Allegra et al (31), calculated MKTs from temperature data loggers placed in drug storage boxes in out-of-hospital vehicles. They showed that excursions above CRT resulted in elevated MKTs even in some climate controlled garages where vehicles with drug boxes were kept. The increase in the MKT from 25 to 30°C could potentially result in a decreased shelf life of up to 43% (31). Church et al (32), examined the degradation of injectable epinephrine (EPI) under constant and cyclical heating conditions. Their

results showed that the thermal stability of injectable EPI was dependant on the method of heat exposure. A constant temperature exposure to 65°C for seven days resulting in complete degradation whereas cyclical heating resulted in a 31% reduction of injectable EPI concentration and a 225% increase in epinephrine sulfonic acid formation (32).

A study conducted by Gammon et al (33), exposed EMS drugs to cyclical temperatures of −6 to +54 °C and sampled active drug concentration at weekly intervals (33). Of significance succinylcholine experienced accelerated decreases in concentration especially when exposed to temperature excursions above label recommendations (82.60±0.67 % of initial concentration remaining on day 14). Stiller (28) and Kupper et al (23) concur that the longer and more extreme the thermal exposure outside recommended storage conditions, the greater probability of a more severe deviation from label conditions. However Kupper et al (23) found that no toxic products occurred from heat induced degradation of succinylcholine. They further noted that frozen ampoules were at risk of developing hairline cracks not visible to the naked eye thus resulting in potential contamination and oxidative degradation of the pharmaceutical product (23). This is of importance when considering packing of drug boxes where ampoules may be placed directly onto frozen cold packs.

1.5 Storage of heat sensitive pharmaceuticals

This section will briefly discuss the storage of heat sensitive pharmaceuticals stored in cold boxes and refrigerators

1.5.1 Cold boxes

At the time of this literature review no recommendations existed for the storage of heat-sensitive pharmaceuticals in cold boxes within the South African theatre environment. The South African national Department of Health Republic of South Africa guidelines on: “Cold Chain and Immunisation Operations Manual”, does not detail specific requirements for the storage of heat-sensitive pharmaceuticals in cold boxes (3). Their recommendations are for use of transport boxes (non-returnable boxes) used by manufacturers to distribute vaccines onwards. Furthermore the authors recommend that

containers should be filled with sufficient ice packs to give the container twice the length of cold life anticipated for a particular journey. Comparatively the WHO (34) list performance specifications for thermally insulated vaccine carriers. Vaccine carriers are referred to as, “carriers used to transport vaccines from health facilities with refrigeration to outreach sessions where refrigeration and ice is unavailable.” The authors describe two types of vaccine carriers, short-range carriers with a minimum cold life of 15 hours and long-range carriers with a minimum cold life of 30 hours**.** Short-range carriers most closely resemble the current storage practices of cold boxes during a typical working day at CHBAH. Cold life is defined by the WHO as, “the empty container is stabilized at +43°C and loaded with ice packs. Cold life is measured from the moment when the container lid is closed until the temperature of the warmest point in the vaccine storage compartment first reaches +10°C, at a constant ambient temperature of +43°C.”(34) Ice pack defined by the WHO as “a water-pack frozen to a temperature between −5°C and −20°C before use.”(34)

1.5.2 Refrigerators

According to the national Department of Health Republic of South Africa, most refrigerators used for vaccine and heat-sensitive pharmaceutical storage in South Africa are domestic type of refrigerators (3). Consequently their innate design was never for the storage of vaccines and heat-sensitive pharmaceuticals but rather for food related products. It is the national Department of Health Republic of South Africa recommendation, that every authority replaces equipment used for the storage of heat-sensitive products with equipment specifically designed for this purpose. McCollester and Vallbona (35), conducted the first graphic-output temperature study quantifying cold chain failure in refrigerators used for the storage of pertussis vaccines in the United States of America. (35) Their findings showed that 48% of the 54 refrigerators sampled over a six day period in Harris County, Texas, maintained their temperatures at the recommended 2 – 8 °C. The remaining percentage of time spent by the refrigerators was freezing (24%), cold (19%) or warm (9%). The authors found that six refrigerators were unable to maintain a stable temperature regardless of thermostat setting and therefore not suitable for the storage of vaccines. It was their observation that

inadequate storage would not have been detected nor quantified without the use of digital temperature data loggers (DLTs). Furthermore the graphic output of the DLTs provided allowed interpretation of temperature data in a manner not possible with traditional twice-daily temperature recordings. The national Department of Health Republic of South Africa guidelines state that the temperature of refrigerators should be read twice daily, first in the morning and last thing in the evening. With a chart kept for each appliance for a six month period (3). As can be seen from the aforementioned study conducted by McCollester and Vallbona (35), refrigerators exhibited varying degrees of thermal performance despite similar monitoring being employed. DLTs therefore provide far greater insight into the thermal performance of a refrigerator over time as opposed to taking dual measurement points.

Anaesthetists are uniquely positioned within the cold chain as end-users of potent heat-sensitive pharmaceuticals. Consequently, the potential for harm to our patients due to non-adherence of basic cold chain principles exists. Importantly the tolerance of heat-sensitive pharmaceutical products to temperature excursions varies considerably and is dependent on numerous factors and furthermore is often difficult to predict or quantify. Additively, manufacturers are not required to report at what temperatures their products are stable at but are rather required to manufacture products stable within environments dictated by their package labelling. Therefore non-adherence to the cold chain through exposure of heat-sensitive pharmaceutical products to temperature excursions may result in compromised pharmaceutical products with reduced potency, differing compound formation and the generation of potentially toxic substances. To the author's knowledge, no studies have been identified that quantify the ambient temperatures and potential temperature excursions experienced by heat-sensitive pharmaceutical products stored in cold boxes within the theatre environment.

SECTION TWO – AUTHORS GUIDELINES

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The following are sample references:

1. Jun BC, Song SW, Park CS, Lee DH, Cho KJ, Cho JH. The analysis of maxillary sinus aeration according to aging process: volume assessment by 3-dimensional reconstruction by high-resolutional CT scanning. Otolaryngol Head Neck Surg. 2005 Mar;132(3):429-34.
2. 2. Polgreen PM, Diekema DJ, Vandeberg J, Wiblin RT, Chen YY, David S, et al. Risk factors for groin wound infection after femoral artery catheterization: a case-control study. Infect Control Hosp Epidemiol [Internet]. 2006 Jan [cited 2007 Jan 5];27(1):34-7. Available from: http://www.journals.uchicago.edu/ICHE/journal/issues/v27n1/2004069/2004069.web.pdf.

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SECTION THREE - DRAFT ARTICLE

Adequacy of the cold chain used for the storage of heat-sensitive pharmaceuticals in a department of anaesthesiology

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Key words:

Cold chain, cold box/drug box, heat-sensitive pharmaceuticals

Abstract

Background

Anaesthesia frequently involves administration of refrigerated intravenous drugs to patients. Often overlooked, maintenance of the cold chain forms a key component of pharmacovigilance for anaesthetists. However the South African national Department of Health guidelines on: "Cold Chain and Immunisation Operations Manual", does not detail specific requirements for medically validated cold boxes. Consequently the risk of iatrogenic harm to patients from heat-sensitive pharmaceuticals in inappropriately temperature regulated cold boxes exists.

Methods

The research design was that of a descriptive, prospective and contextual study. Part I study population comprised the ambient air temperatures of the refrigerator and cold boxes used for storage of heat-sensitive pharmaceuticals in theatre at CHBAH over eight hours. Part II study population was newly purchased cold boxes and cold packs for the purpose of assessing individual cold box thermal performance over eight hours.

Results

In Part I, only a single cold box (polystyrene box number 19) was able to maintain the recommended temperature range of 2 − 8°C for the eight hour period (4.35%). The refrigerator temperature time plot showed a significant deviation of temperature at approximately 30 minutes.

In Part II, only fabric and polystyrene cold boxes with three cold packs in situ were able to maintain the recommended temperature of 2 − 8°C.

Conclusion

This study highlighted the failure of non-medically validated cold boxes to reliably maintain the temperature of heat-sensitive pharmaceuticals.

Introduction

Anaesthesia frequently involves administration of potent intravenous drugs to patients. Anaesthetists therefore assume responsibility for the inherent complications associated with all iatrogenic reactions, both benign and malignant. The United States Pharmacopeia's (USP) Medmarx® medication-error reporting system has reported nearly 1000 incidences involving errors associated with refrigerated medications, many of which attributable to the inappropriate storage of medications. [5] Consequently, reduction in iatrogenic harm has been recognised as a priority in healthcare. Pharmacovigilance is defined as, "the science and activities concerned with the detection, assessment, understanding and prevention of adverse reactions to medicines (i.e. adverse drug reactions or ADRs). The ultimate goal of this activity is to improve the safe and rational use of medicines, thereby improving patient care and public health." [2] Therefore, pharmacovigilance constitutes a vital component in the practice of safe anaesthesia.

A key, yet often overlooked area of pharmacovigilance, particularly within the scope of anaesthesia, pertains to the cold chain. The cold chain can be defined as, "A system consisting of people, equipment and heat-sensitive pharmaceuticals such as vaccines, which ensures that the correct quantity of potent vaccine/medicine reaches the children, women or men who need it. The temperature of these items must be maintained within a specified temperature range from the time of production through to the administration thereof." [3]

To guarantee that pharmaceuticals are delivered to patients without any loss of therapeutic efficacy has always been a concern for the pharmaceutical industry. [4] This is a statement that particularly holds true in the case of heat-sensitive pharmaceuticals. Degradation of these drug products is dependent on factors such as: physical and chemical properties of the ingredients, interaction between active and inactive ingredients, container closure system, environmental conditions encountered during shipment and storage and handling as well as length of time between manufacture and usage. [13] The consequence of non-adherence to the basic principles of cold chain management is potentially reduced potency, different compound formation within the drug product and the generation of toxic substances. [15]

Temperature has been described as the single most important factor involved in drug degradation. [14] It is on this basis that regulatory authorities like the World Health Organisation, USP, International Congress on Harmonisation and the Parenteral Drug Association require manufacturers to conduct stability tests in order to determine the recommended temperature ranges that maintain the stability of the heat-sensitive pharmaceutical during shipment, handling, storage and ultimately dictate the products shelf-life and expiry date. Pharmaceutical manufacturers are not required to report at what temperatures their products are stable, but are required only to manufacture products stable within the environments dictated by their package labelling. [26] This is in accordance with the USP Chapter <1079> Good Storage and Distribution Practices. [11] However, the products tolerance for short and long-term exposure to temperatures beyond those specified by the manufacturers may vary widely. [12] A study conducted by Gammon et al [33], showed accelerated decreases in concentrations of succinylcholine especially when exposed to

temperature excursions above label recommendations. Furthermore, manufacturers do not detail the specific issues of heat cycling, temperature excursions and freeze-thawing of heat-sensitive pharmaceuticals and as such a paucity of information pertaining to heat-sensitive pharmaceuticals stored in cold boxes exists. It is therefore paramount that the recommended temperature ranges for heat-sensitive pharmaceuticals be adhered to.

The South African national Department of Health guidelines on: "Cold Chain and Immunisation Operations Manual", does not detail specific requirements for medically validated cold boxes. [3] Their recommendations are for use of transport boxes (non-returnable boxes) used by manufacturers to distribute vaccines onwards. Currently, no detailed recommendations exist for the storage of heat-sensitive pharmaceuticals within theatre cold boxes. Literature pertaining to the use of cold boxes for the storage of heat-sensitive pharmaceuticals in theatre does not exist. Thus anaesthetists, although uniquely positioned at the end of the cold chain, represent a crucial link in the maintenance of the cold chain given the storage practices of anaesthetists in South African theatres.

Little is known with regard to the adequacy of the cold chain and the potentially damaging environment that heat-sensitive pharmaceuticals may be exposed to within cold boxes. We therefore undertook a two-part study. The aim of the first part of the study was to describe the adequacy of the cold chain used for the storage of heat-sensitive pharmaceuticals in the Department of Anaesthesiology at Chris Hani Baragwanath Academic Hospital (CHBAH). The aim of the second part of the study was to quantify the thermal performance of the different types of cold boxes used in the University of the Witwatersrand Department of Anaesthesiology, using newly purchased cold boxes and cold packs.

Methodology

The research design was that of a descriptive, prospective and contextual study. This study did not involve any human subjects therefore an ethics waver to conduct the study was obtained from the Human Research Ethics (Medical) Committee of the University of the Witwatersrand.

The study population for Part I included the refrigerator, cold boxes and cold/cool packs used in theatre. The study population for Part II included the newly purchased cold boxes and cold packs for the purpose of assessing cold box thermal performance. Purposive sampling was used for the study. No studies have been identified internationally or nationally on the use of cold boxes for the storage of heat-sensitive pharmaceuticals within theatre to help guide sample size determination. The sample size for Part I consisted of the refrigerator and all 23 cold boxes and their associated cold/cool packs. The reason for using the total cold box population was that the thermal performance of cold boxes varied amongst the different types of boxes used in theatre and was dependent on extraneous factors i.e. type of box and condition, cold/cool packs used, packing method employed, etc. It would therefore be difficult to extrapolate findings from a smaller sample group. The sample size for Part II consisted of 12 boxes (four of each of the three types: fabric, polystyrene and hard plastic) and 30 cold packs. This was done over a seven-day period which gave a total of 84 temperature recordings.

Part I of data collection

All cold boxes used for the storage of heat-sensitive pharmaceuticals were prepared by each theatres registrar before the commencement of the list. This occurred at approximately 07:30 in the morning with registrars collecting drug boxes, cold/cool packs and heat-sensitive pharmaceuticals from the refrigerator in theatre.

Thus, for the purpose of this study all cold boxes were collected prior to their preparation and each given a unique number for reference and identification purposes. The cold boxes were then described in terms of their defining characteristics. The subsequent findings were captured on a data collection sheet.

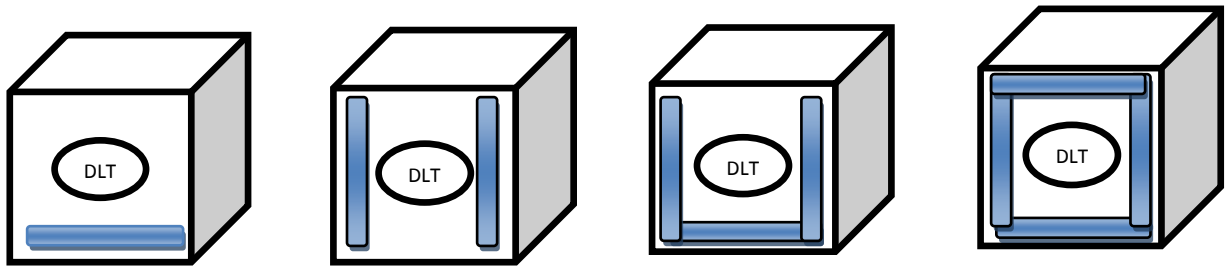
Temperature data loggers (DLTs) were secured in each of the cold boxes on the bottom centre of the cold box prior to the addition of cold/cool packs and drugs (likely coldest point in the cold box) at approximately 07:15. Additively a DLT was placed in the refrigerator used for the storage of heat-sensitive pharmaceuticals and cold packs in theatre. The DLTs remained in the cold boxes and refrigerator until the completion of the theatre day, concluding 16:00 when they were collected. Data from all DLTs was subsequently downloaded and analysed at a later date. Simultaneously after the temperature probes were collected, a description of the number of cold packs as well as the manner in which the cold boxes were packed was added to the data collection sheet.

The data collection sheet was devised to record the data: refrigerator type and temperature, type of cold box (fabric, polystyrene, hard plastic), physical appearance/condition, dimensions (length x width x height and litre), cold box ambient air temperature, type of cold/cool pack, number of cold packs placed in situ and packing method employed. Photographic evidence of each of the cold boxes was taken before each inspection, attached to the data collection sheet and included in an appendix of the final report. The data was collected personally by one author (GB) and entered into a Microsoft Excel© 2013.

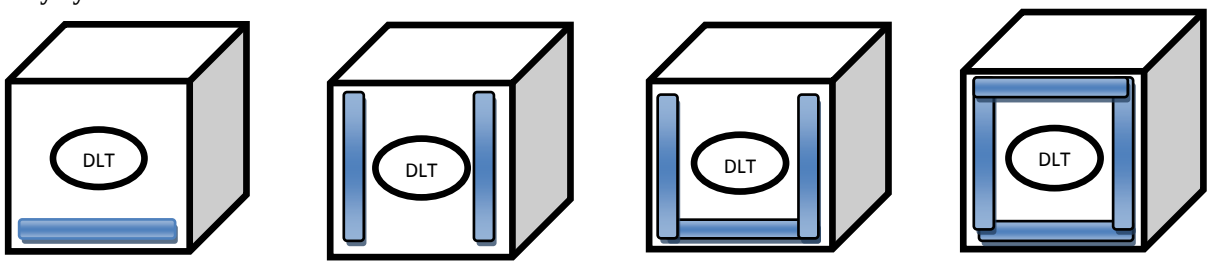
Part 2 of data collection

A total of 12 cold boxes and 30 cold packs were used for Part II of the study. Four of each type of cold box (fabric, polystyrene and hard plastic) was used. In each type of cold box, subgroups containing 1, 2, 3 or 4 cold packs and a DLT were placed in the bottom centre of the cold box and the lid closed. The cold boxes were exposed to a constant room temperature of 21 − 23°C and the ambient air temperature in each of the 12 cold boxes measured from 08:00 to 16:00 (Figure I). Temperatures within the 12 boxes were measured over a seven-day consecutive period resulting in a total of 84 samples.

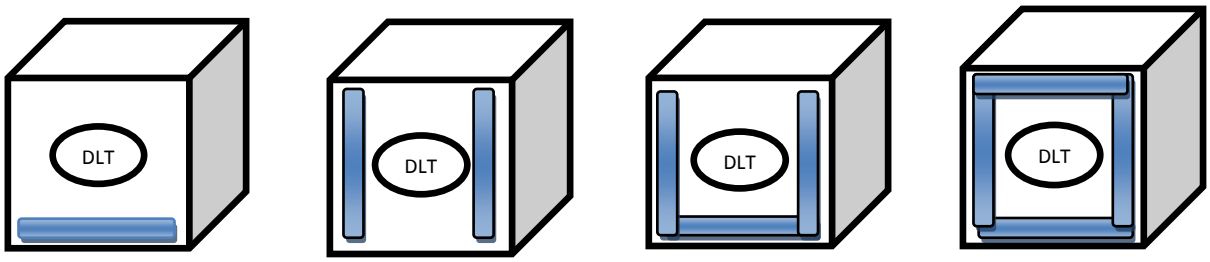
Fabric cold boxes



Polystyrene cold boxes



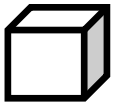
Hard plastic cold boxes



Key:

Cold pack

Data logger temperature



Cold box

Figure I Three types of cold boxes (fabric, polystyrene and hard plastic) with their respective subgroups of 1, 2, 3 or 4 cold packs and DLT in situ.

All data collected was analysed in consultation with a biostatistician using GraphPad Prism 7 statistical program. Descriptive and inferential statistics were used to analyse the data. Categorical variables were described using frequencies and percentages. Continuous variables were described using means and standard deviations or medians and interquartile ranges depending on the distribution of the data. In Part II of the study, ANOVA was used to compare thermal performance of the cold boxes and their cold packs. A p value of <0.05 was considered statistically significant.

RESULTS

Part I

The refrigerator at CHBAH used for the storage of heat-sensitive pharmaceuticals is a Husky® commercial grade refrigerator with two pull open doors. A single mercury thermometer placed within the refrigerator allows for temperatures to be manually recorded twice daily on a chart located on the outside of the refrigerator. No visual display of temperature, open-door alarm or intrinsic backup power supply to the refrigerator was observed. There was however a backup power supply in the form of a diesel electric generator which supplies the hospital as well as a secondary uninterrupted power supply unit. Figure II shows the ambient air temperatures measured within the refrigerator from a sample collected on the 19 September 2016 from 08:00 to 16:00 (eight hours).

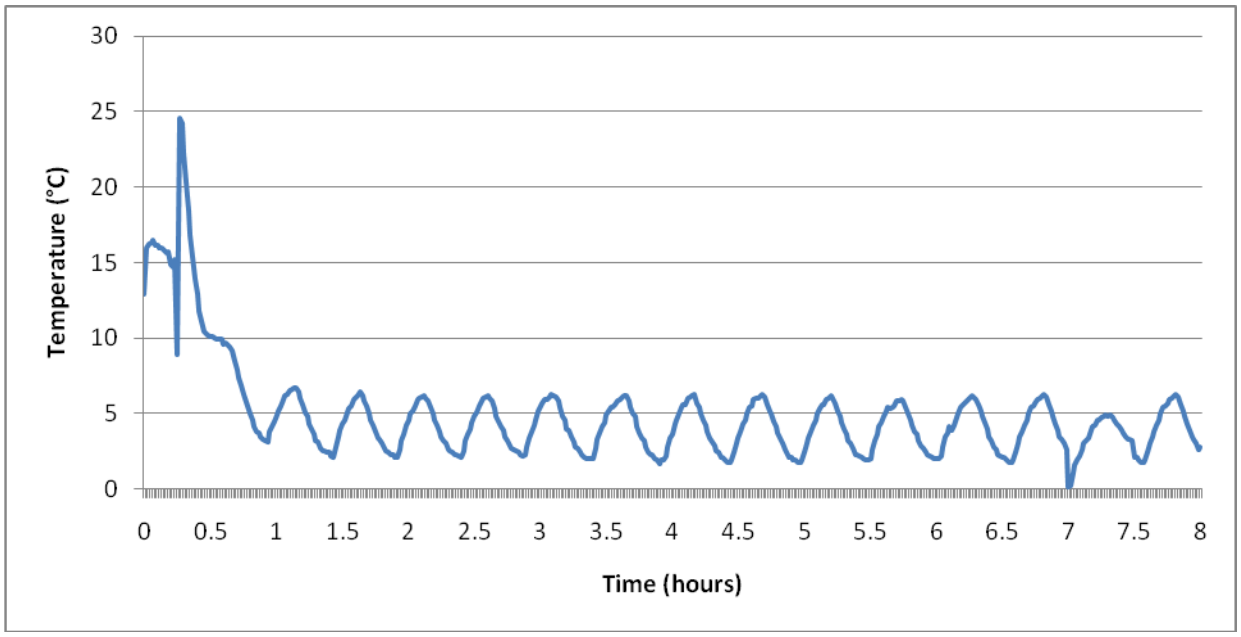


Figure II Refrigerator temperatures over eight hours

Table I depicts the population demographics of the cold boxes and their cool/cold packs. A total of 17 fabric (73.91%) and six polystyrene (26.09%) were sampled. Seven fabric (41.17%) and two polystyrene (33.33%) cold boxes were found to be damaged. Seventeen (73.91%) of the cold boxes were found open on collection of the DLTs at the end of the theatre day. The 35 cool/cold packs sampled consisted of 21 cool packs and 14 cold packs. Only seven (50%) of the cold packs were frozen prior to their use. None of the cold packs were appropriately prepared i.e. wrapped in bubble wrap. The registrars employed a haphazard approach (43.47%) to packing of the cold boxes or simply rested the heat-sensitive pharmaceuticals on top (47.82%) of, or underneath (4.35%) the cold/cool pack. No temperature monitoring devices were found in addition to the DLTs used.

Table I Chris Hani Baragwanath theatre cold box convenience sample

Theatre sample no	Type of cold box used	Cold box dimensions cm (length x width x height)	Volume in litres	Condition of cold box	Open or closed cold box	Type of cold/cool pack used	No of packs inside cold box	Manner in which cold box packed
1	Fabric	26x15x10	3.9	Zip broken lining intact	Open	Cool pack	1	Haphazard
2	Fabric	26x15x10	3.9	Zip broken lining intact	Open	Cool pack	2	Haphazard
3	Fabric	20x15x15	4.5	Grossly intact	Closed	Cold pack	1	Cold pack resting in receiver with drugs
4	Fabric	20x15x15	4.5	Grossly intact	Open	Cool pack	1	Drugs resting on top of cool pack
5	Fabric	20x15x12	3.6	Grossly intact	Open	Cold pack not frozen	1	Haphazard
6	Fabric	22x15x15	4.95	Damaged lining	Open	Cool pack	1	Haphazard
7	Fabric	22x15x12	3.96	Damaged lining	Open	Cool pack	1	Haphazard
8	Fabric	22x15x15	4.95	Grossly intact	Open	Cool pack	1	Drugs resting on top of cool pack
9	Fabric	21x15x15	4.725	No zip	Open	Cold pack not frozen	1	Drugs underneath cold pack
10	Fabric	20x15x15	4.5	Grossly intact	Open	Cool pack & Cold pack not frozen	1 1	Drugs resting on top of cool pack
11	Fabric	20x15x15	4.5	Grossly intact	Open	Cool pack	1	Haphazard
12	Fabric	20x15x15	4.5	Grossly intact	Open	Cool pack	2	Haphazard
13	Fabric	22x15x15	4.95	Grossly intact	Open	Cool pack & Cold pack not frozen	1 1	Haphazard
14	Fabric	20x15x12	3.6	Grossly intact	Open	Cool pack	2	Drugs resting on top of cool pack
15	Fabric	20x13x12	3.12	Grossly intact	Closed	Cool pack	1	Haphazard
16	Fabric	15x15x15	3.375	Damaged lining	Open	Cool pack	1	Drugs resting on top of cool pack
17	Fabric	21x15x12	3.78	Lining damaged	Open	Cool pack	1	Haphazard
18	Polystyrene	26x15x19	7.41	Right corner damage	Closed	Cool pack & Cold pack not frozen	1 2	Drugs resting on top of cool pack
19	Polystyrene	26x15x19	7.41	Grossly intact	Closed	Cold pack frozen	3	Drugs resting on top of cool pack
20	Polystyrene	26x15x19	7.41	Grossly intact	Open	Cool pack	1	Drugs resting on top of cool pack
21	Polystyrene	26x15x19	7.41	Grossly intact	Closed	Cold pack frozen	2	Drugs resting on top of cool pack
22	Polystyrene	26x15x19	7.41	Grossly intact	Closed	Cold pack frozen	2	Drugs resting on top of cool pack
23	Polystyrene	26x15x19	7.41	Left corner damage	Open	Cool pack	2	Drugs resting on top of cool pack

The ambient air temperature measured in each of the 23 cold boxes over an eight- hour period is shown in Figure III.

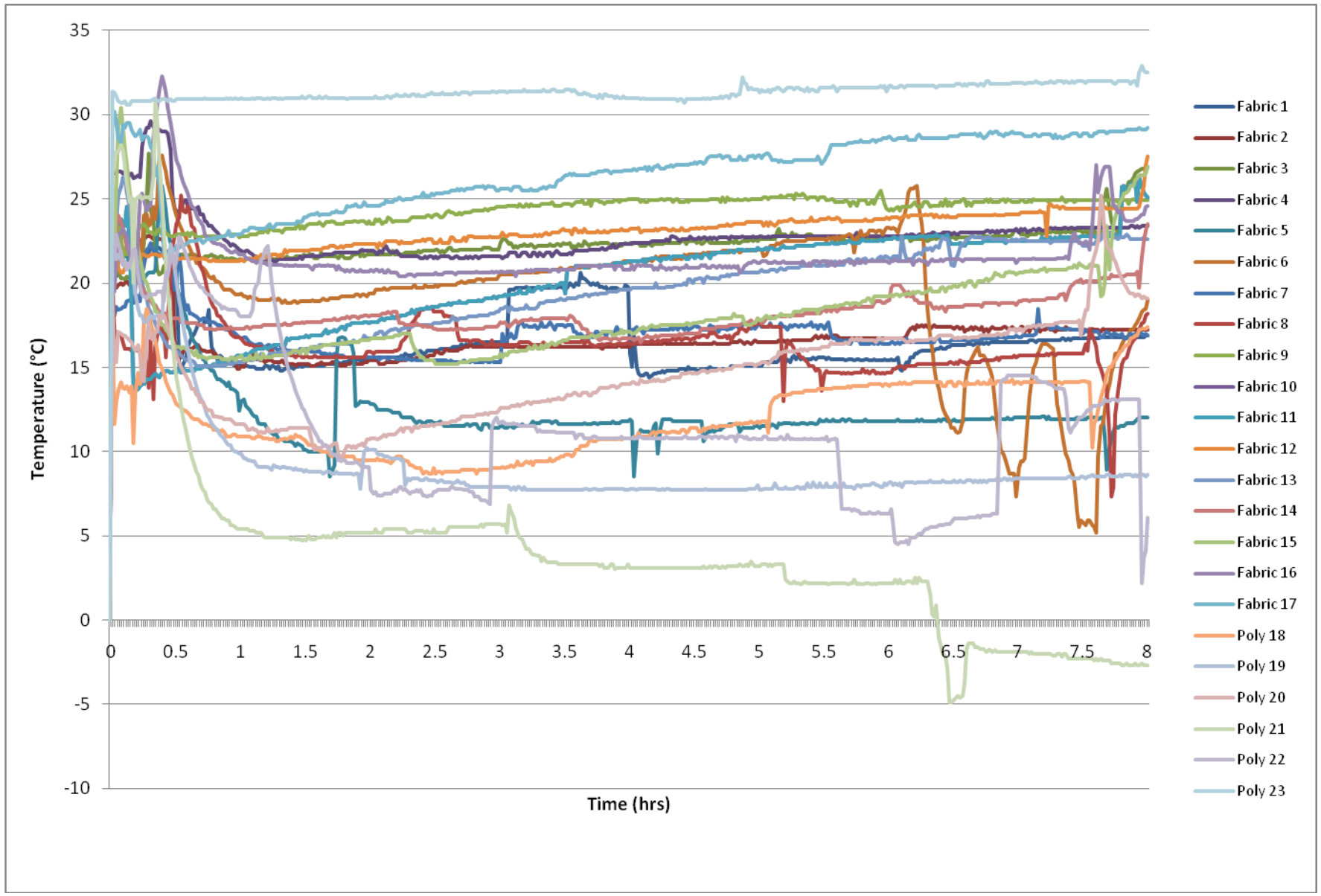


Figure III Ambient air temperatures measured in 23 theatre cold boxes

The following Figures IV – VI, contrast the mean temperatures recorded in the three different types of cold boxes and their respective subgroups (1, 2, 3, and 4 cold packs in situ) at 20-minute intervals. The ambient air temperature within each of the cold boxes was recorded over an eight-hour period for seven consecutive days. Steady state was reached at the sixth 20-minute interval (two hours) depicted by the blue line in each figure below.

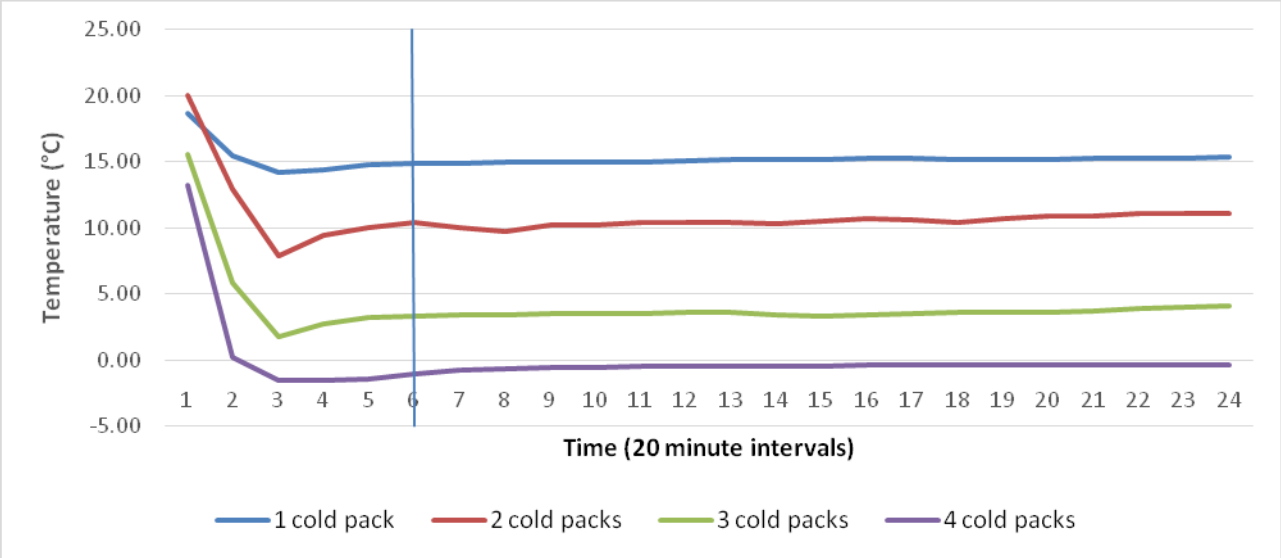


Figure IV Mean fabric cold box temperatures at 20-minute intervals with 1, 2, 3 and 4 cold packs over a seven day period

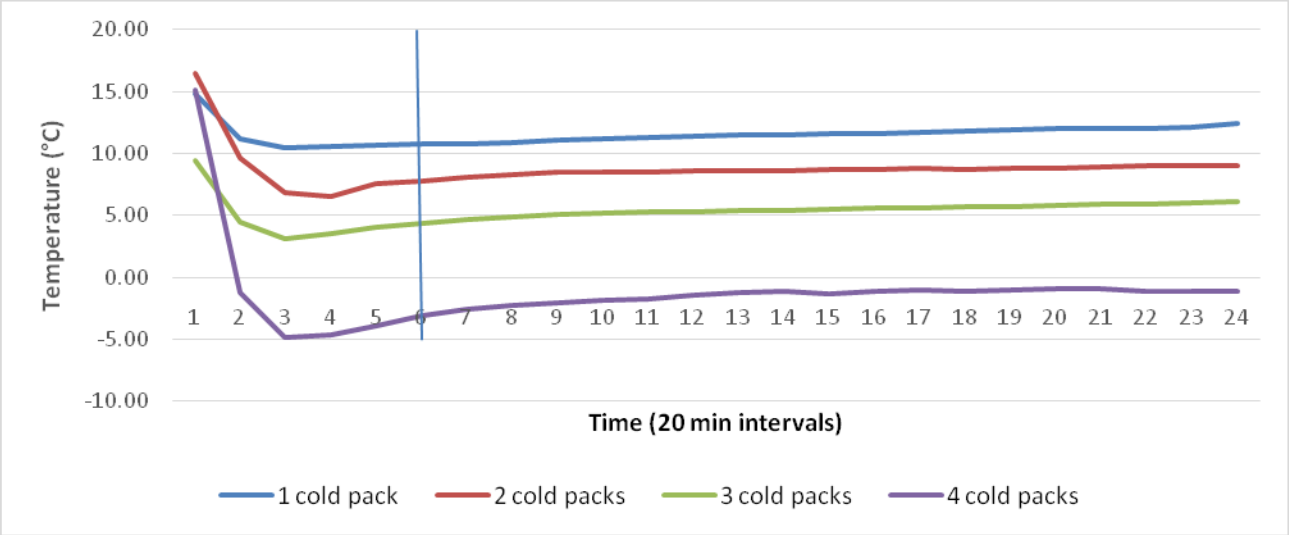


Figure V Mean polystyrene cold box temperatures at 20-minute intervals with 1, 2, 3 and 4 cold packs over a seven day period

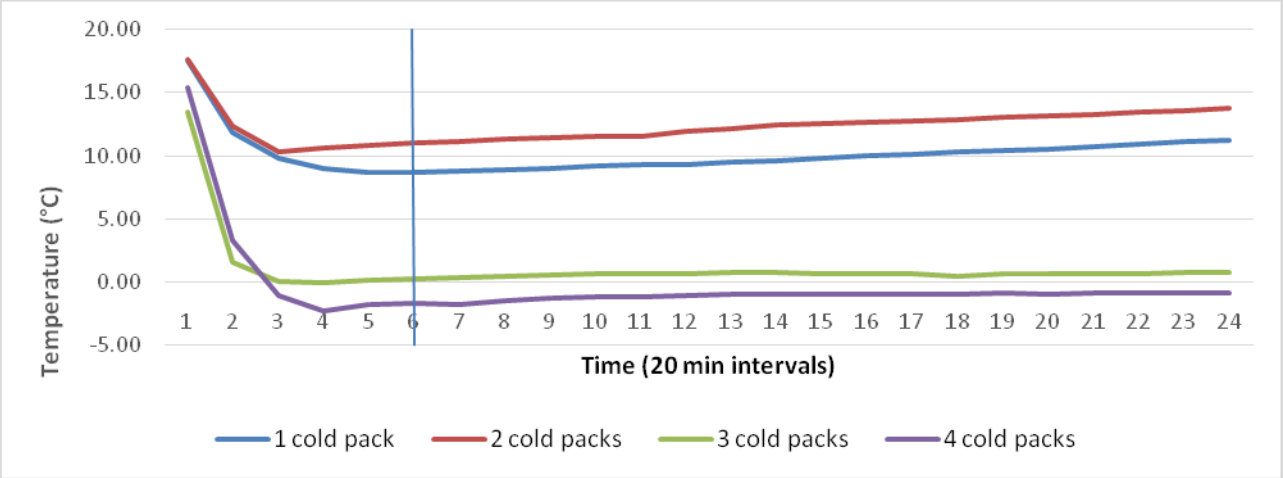


Figure VI Mean hard plastic cold box temperatures at 20-minute intervals with 1, 2, 3 and 4 cold packs over a seven day period

Table II compared the thermal performance of the various types of cold boxes and the effect of varying number of cold packs in situ. There was a significant drop in cold box temperature within the first two hours (sixth interval). Therefore, mean temperature analysis was conducted at 20-minute intervals after steady state of temperature was achieved.

A Tukey post-hoc test and ANOVA showed that within each of the four cold box subgroups significant differences existed between the fabric, polystyrene and hard plastic cold boxes; $p < 0.05$.

Table II Comparison of mean cold box ambient temperatures

Subgroup	Fabric Mean (SD)	Polystyrene Mean (SD)	Hard plastic Mean (SD)	P value
1 cold pack	15.1 (0.15)°C	11.6 (0.48)°C	12.4 (0.88)°C	< 0.0001
2 cold packs	10.53 (0.38)°C	8.6 (0.31)°C	9.5 (0.81)°C	< 0.0001
3 cold packs	3.59 (0.21)°C	5.5 (0.47)°C	0.58 (0.14)°C	< 0.0001
4 cold packs	-0.49 (0.18)°C	-1.47 (0.6)°C	-1.14 (0.27)°C	< 0.0001

Table III represents the mean number of ambient air temperatures at steady state which were found to be within the recommended refrigeration range of 2 − 8°C from the sixth interval (2 hours).

Table III Mean cold box ambient air temperatures

Temperature	Fabric				Hard Plastic				Polystyrene			
	Number of cold packs											
	1	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
2 - 8°C	0	0	19	0	0	0	0	0	0	1	19	0
<2°C & >8°C	19	19	0	19	19	19	19	19	1	18	0	19

Of note only the fabric and polystyrene cold boxes with three cold packs in situ were able to maintain the recommended ambient air temperature of 2 − 8°C i.e. the Goldilocks range.

Discussion

To date, no studies have been identified that quantify the ambient air temperatures experienced by heat-sensitive pharmaceutical products stored in cold boxes for use within theatre. However, it is common practice for the anaesthetic registrars at University of the Witwatersrand, to collect and store heat-sensitive pharmaceuticals in cold boxes for use within theatre prior to their administration to patients.

In Part I of the study conducted at CHBAH theatre complex, only one polystyrene box (number 19) was able to maintain the recommended goldilocks temperature range of 2 − 8°C for the eight-hour working day (4.35%). Of the remaining 22 cold boxes, only one other polystyrene cold box (number 21) was able to decrease the ambient air temperatures below 8°C. The remaining cold box temperatures were found to increase throughout the day in response to the external ambient theatre temperature and diminishing effect of the cold/cool packs. This could be attributable to a number of factors.

Firstly, many of the cold boxes used were found to be in a state of disrepair. A total of seven fabric cold boxes (41.17%) were significantly damaged i.e. zip broken or silver lining on the inside was damaged. This made them essentially unusable. Of the six polystyrene cold boxes, two were damaged (33.33%) at the corners making integrity of the cold box null and void. This was echoed by the poor thermal performance of these polystyrene cold boxes (numbers 18 and 23).

Secondly, 74% of cold boxes were found to be open on collection of the DLTs at the end of the theatre day. This was partially attributable to damaged fabric cold boxes with broken zips as well as user error. Of note, polystyrene box number 23 maintained a constant ambient temperature of greater than 30°C for the entire eight hour period,

probably as a result of never being closed and therefore equilibrating with the ambient theatre temperature. These markedly elevated temperatures represent major deviations from regulatory [3, 7-11] and pharmaceutical manufacturer's recommendations. Consequently, this could have catastrophic effects for the heat-sensitive pharmaceuticals.

Thirdly, varying types, numbers of cold/cool packs and packing methods of the cold boxes were employed. None of which conform to the validated criteria used for the storage of heat-sensitive pharmaceuticals as per the South African national Department of Health guidelines and World Health Organization. [3, 7] Cool packs refrigerated to 2 − 8°C, as opposed to cold packs frozen to −5°C to −20°C were used to cool the cold boxes. Cool packs refrigerated to 2 − 8°C have a lesser ability to effectively cool the cold box down to the recommended storage temperature of 2 − 8°C owing to their lower thermal mass. [19] The cold packs that were used were often not frozen (50%) and therefore functioned as cool packs. None of the cold packs were found to be prepared in accordance with the South African national Department of Health guidelines i.e. allowed to sweat/precipitate and then wrapped in bubble wrap. [3] The registrars employed a haphazard approach (43.47%) to packing of the cold boxes or simply rested the heat-sensitive pharmaceuticals on top (47.82%) of, or underneath (4.35%) the cold/cool pack. Compounding this problem these heat-sensitive pharmaceuticals were often found out of their respective secondary packaging. Thus, the risk of direct contact of primary packaging/ampoule and cold pack could occur. Of note, the DLT in polystyrene box number 21 experienced a considerable drop in temperature well below freezing. This is likely attributable to the probe coming into direct contact with a frozen cold pack incorrectly prepared. This not only poses the immediate problem of lack of usability e.g. in an emergency situation [20-22], but could lead to loss of sterility from hairline crack formation, reduced potency from oxidation, instability and denaturing of excipients/solutes/proteins. [23]

Examination of the commercial refrigerator temperature time plot shows the cycle nature of temperature at 2 − 8°C. However an important deviation of temperature occurred at approximately 08:00 (increase in temperature to 25°C). This could be due to either the repeated opening of the refrigerator doors by registrars collecting heat-sensitive pharmaceuticals or from the doors being held open when restocking the refrigerator. These fluctuations in temperature are likely missed in this non-medically validated commercial refrigerator, as no visual display of temperature, open-door/temperature alarm or DLT is in situ. It is questionable whether such a short temperature excursion would have had a profound negative impact on heat-sensitive pharmaceuticals. However, without a longer recorded history of events quantifying the duration and severity of the temperature excursions, it would be impossible to draw a conclusion. Future studies could explore this further.

In Part II of the study, thermal performance of each the three types cold boxes (fabric, polystyrene and hard plastic) with varying numbers of cold packs (one, two, three and four) was assessed. Comparison of the mean ambient air temperatures at 20 minute intervals after steady state (2 hours) revealed that only the fabric and polystyrene cold boxes with three cold packs in situ were able to maintain the recommended temperature of 2 − 8°C i.e. goldilocks range. A potential explanation for the hard plastic cold box not exhibiting the same thermal performance is due to its

differing volume and thermal insulation properties. Two cold packs in situ resulted in a mean ambient air temperature of 9.5°C, however a critical cooling point was reached with three cold packs in situ, effectively dropping the ambient air temperature to 0.58°C (near freezing). Addition of a fourth cold pack to all three cold box types resulted in a similar trend of ambient air temperature below freezing. It should be noted that these ambient air temperatures recorded in cold boxes were under ideal operational conditions i.e. cold boxes were not opened during the eight hour sampling period and the external ambient temperature was held constant at 21 − 23°C for the duration of testing. Future studies could explore the effect of repeated opening and closure on the ambient cold box temperature.

Conclusion

This study at Chris Hani Baragwanath Academic Hospital highlighted the failings of current systems and structures employed to maintain the cold chain within cold boxes used for the storage of heat-sensitive pharmaceuticals. Non-medically validated cold boxes do not reliably maintain the temperature of heat-sensitive pharmaceuticals and therefore the safety and efficacy of heat-sensitive pharmaceuticals cannot be guaranteed. The authors recommend medically validated cold boxes. However in a setting where not available, polystyrene or fabric cold boxes with three appropriately prepared cold packs in situ may be substitutable. The authors found that plastic cold boxes did not reliably maintain the recommended cold box temperature irrespective of the number of cold packs placed in situ. The authors strongly recommend the use of medically validated refrigerators for the storage of heat-sensitive pharmaceuticals. This is in keeping with the Department of Health Cold Chain and Immunisations Manual. It is therefore the inherent responsibility of all persons involved when using heat-sensitive pharmaceuticals to take cognisance of the importance of the cold chain and the potential detrimental effect non-adherence may have on heat-sensitive pharmaceuticals and the patients who receive them.

Conflict of interest

We declare that we have no financial or personal relationships which may have inappropriately influenced us in writing this paper.

Acknowledgements

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References

1. Santell J, Hicks R, McMeekin J, Cousins D. Medication errors: Experience of the United States Pharmacopeia (USP) MEDMARX Reporting System. J Clin Pharmacol. 2003;43(7):760 - 7.

2. WHO. Pharmacovigelence Guidelines [12 January 2014]. Available from: http://www.who.int/medicines/areas/quality_safety/safety_efficacy/S.AfricaDraftGuidelines.pdf.

3. Department of Health. Cold Chain and Immunisation Operations Manual: Guidelines for Handling Heat Sensitive Vaccines and Pharmaceuticals. South Africa.2015. Available from: http://www.health.gov.za/index.php/2014-08-15-12-53-24?download=2573:cold-chain-and-immunisation-operations-manual.

4. Ammann C. Stability studies needed to define the handling and transport conditions of sensitive pharmaceutical or biotechnical products. AAPS J. 2011;12(4):1264 - 75.

5. Rubiana F, Wanderley P. Storage conditions for stability testing of pharmaceuticals in hot and humid regions. Drug Dev Ind Pharm. 2007;33(4):393 - 401.

6. Florence A, Attwood D (2011). *In Principios Fisicos Quimicos em Farmacia (2nd Edition)*.Sao Paulo. Pharmabooks.

7. Kommanaboyina B, Rhodes C. Trends in stability testing, with emphasis on stability during distribution and storage. Drug Dev Ind Pharm. 1999;25(7):857 - 68.

8. Brown LH, Krumperman K, Fullager J. Out-of-hospital medication storage temperatures: A review of literature and directions for the future. Prehosp Emerg Care. 2004;8(2):200 - 7.

9. Ziance R, Chandler C, Bishara R. Integration of temperature-controlled requirements into pharmacy practice. J Am Pharm Assoc. 2009;49(3):61 - 9.

10. Gammon DL, Su S, Jordan J, Patterson R, Finley PJ, Lowe C, et al. Alteration in prehospital drug concentration after thermal exposure. Am J Emerg Med. 2007;26(5):566 - 73.

11. WHO. Good distribution practices for pharmaceutical products. Technical Report Series. 2010;No 957(Annex 5). Available from: http://www.who.int/medicines/areas/quality_safety/quality_assurance/GoodDistributionPracticesTRS957Annex5.pdf

12. Stability testing of new drug substances and products - Q1A (R2) International Conference on Harmonization.; 6 February 2003. Available from: http://www.ich.org/products/guidelines/quality/quality-single/article/stability-testing-of-new-drug-substances-and-products.html.

13. PDA. Technical Report no. 39: Cold chain guidance for medicinal products: maintaining the quality of temperature-sensitive medicinal products through the transportation environment. Originally published 2005, revised 2007. Available from: https://www.pda.org/publications/pda-publications/pda-technical-reports.

14. PDA. Technical Report no. 46: Last Mile: guidance for the good distribution practices for pharmaceutical products to the end user. 2009. Available from: https://www.pda.org/publications/pda-publications/pda-technical-reports.

15. US Pharmacopoeia - National Formulary [USP 39 NF 34]. Rockville, Md.2016.

16. Seevers R, Ulrich D, Bishara R. The use of mean kinetic temperature (MKT) in the handling, storage, and distribution of temperature sensitive pharmaceuticals. Pharmaceutical Outsourcing: Cold Chain. 2009(10):12 - 6.

17. Emmons S, Abeyewardene L, Ramakrishan U. Case of frozen thiopental. Anesth Analg. 1998;87(3):748.

18. Stone J, Fawcett W. A case of frozen succinylcholine encountered. Anesth Analg. 2002;95(5):1465.

19. Kumarvel V. Frozen succinylcholine. Anaesthesia. 2006;61(2):190 - 202.

20. Kupper T, Schraut B, Rieke B, Hemmerling AV, Schoffl V, Steffgen J. Drugs and drug administration in extreme environments. J Travel Med. 2006;13(1):35 - 47.

SECTION FOUR - APPENDICES

4.1 Ethics Approval

Human Research Ethics Committee (Medical)

Research Office Secretariat: Senate House Room SH 10005, 10th floor. Tel +27 (0)11-717-1252
Medical School Secretariat: Medical School Room 10M07, 10th Floor. Tel +27 (0)11-717-2700
Private Bag 3, Wits 2050, www.wits.ac.za. Fax +27 (0)11-717-1265

Ref: W-CJ-140303-2 03/03/2014

TO WHOM IT MAY CONCERN:

Waiver: This certifies that the following research does not require clearance from the Human Research Ethics Committee (Medical).

Investigator: Dr G A Boy (student no. 0603288M).

Project title: Adequacy of the cold chain used for the storage of the sensitive pharmaceuticals in a department of anaesthesiology

Reason: This is a non-human study to assess the thermal performance of cold chain used for the storage of heat-sensitive pharmaceuticals in the Chris Hani Baragwanath Academic Hospital operating theatres. Written permission to do the study from the Chris Hani Baragwanath Academic Hospital CEO must be lodged with the HREC(Medical) Secretariat for the Committee's records.

UNIVERSITY OF THE WITWATERSRAND
PROF PE CLEATON - JONES
HREC (MEDICAL)
2014 -03- 03
JOHANNESBURG

Professor Peter Cleaton-Jones

Chair: Human Research Ethics Committee (Medical)

Copy - HREC(Medical) Secretariat : Anisa Keshav, Zanele Ndlovu.

SECTION FIVE - PROPOSAL

ADEQUACY OF THE COLD CHAIN USED FOR THE STORAGE OF HEAT-SENSITIVE PHARMACEUTICALS IN A DEPARTMENT OF ANAESTHESIOLOGY

Name: Graham Anthony Boy

Student No: 0603288M

Supervisors: **Mrs J. Scribante**

Department of Anaesthesiology

Co-Supervisor: **Dr T. Kleyenstuber**

Department of Anaesthesiology

1. Introduction

Anaesthesia frequently involves administration of potent intravenous drugs to patients. Medication errors are common in health care systems and reported to be the seventh most common cause of death overall (1). Consequently, reduction in iatrogenic harm has been recognised as a priority in healthcare. Pharmacovigilance is defined as, “the science and activities concerned with the detection, assessment, understanding and prevention of adverse reactions to medicines (i.e. adverse drug reactions or ADRs). The ultimate goal of this activity is to improve the safe and rational use of medicines, thereby improving patient care and public health.” (2) Therefore it constitutes a vital component in the practice of safe anaesthesia.

A key area of pharmacovigilance, particularly within the scope of anaesthetic practice, pertains to the cold chain. The cold chain can be defined as, “A system consisting of people, equipment and heat-sensitive pharmaceuticals such as vaccines, which ensures that the correct quantity of potent vaccine/medicine reaches the children, women or men who need it. The temperature of these items must be maintained within a specified temperature range from the time of production through to the administration thereof.”(3)

It has been reported by the Intercontinental Marketing Services (IMS) Institute for Healthcare Informatics that the pharmaceutical market could reach nearly 1 200 billion US dollars by 2016. Furthermore, in “pharmerging markets” (of which South Africa is considered a part) spending will increase by 10% to 30% of global spending over the next five years (36). What percentage of the aforementioned pharmaceutical market constitutes heat-sensitive pharmaceuticals is unknown; however the IMS Institute for Healthcare Informatics report vaccines accounting for a projected cost of 19 – 22 billion US dollars in 2016, or approximately 2%. Thus heat-sensitive pharmaceuticals constitute a significant proportion of a countries health care budget. Failure to adhere to

the principles of the cold chain carries not only financial implications, but also to patient safety as well.

To guarantee drugs are delivered to patients without any loss of therapeutic effect has always been a major concern for the pharmaceutical industry (4). This is a statement that particularly holds true in the case of heat-sensitive pharmaceuticals. Degradation of these drug products is dependent on numerous factors such as: physical and chemical properties of the ingredients, interaction between active and inactive ingredients, container closure system, environmental conditions encountered during shipment and storage and handling as well as length of time between manufacture and usage (13). The consequence of lack of adherence to the basic principles of cold chain management is potentially reduced potency, different compound formation within the drug product and the generation of toxic substances (15).

There are an increasing number of therapeutic pharmaceuticals requiring temperature control and it is temperature that has been described as the single most important factor involved in drug degradation (14). It is on this basis that the Food and Drug Administration regulations require manufacturers to conduct stability tests in order to determine the recommended temperature ranges that maintain the stability of the heat-sensitive pharmaceutical during shipment, handling, storage and ultimately dictate the products shelf-life and expiry date. However pharmaceutical manufacturers are not required to report at what temperatures their products are stable, but are required only to manufacture products stable within the environments dictated by their package labelling (26). This is in accordance with the United States Pharmacopeia (USP) Chapter <1079> Good Storage and Distribution Practices. However the products tolerance for short and long-term exposure to temperatures beyond those specified by the manufacturers may vary widely (12). It is therefore critical that the recommended temperature ranges for heat-sensitive pharmaceuticals be adhered to. This is of particular importance when considering the potential effect of temperature excursions within storage practices at Chris Hani Baragwanath Academic Hospital Department of Anaesthesiology.

The South African national Department of Health guidelines on: “Cold Chain and Immunisation Operations Manual”, does not detail specific requirements for medically validated cold boxes (3). Their recommendations are for use of transport boxes (non-returnable boxes) used by manufacturers to distribute vaccines onwards. Currently, no detailed recommendations exist for the storage of heat-sensitive pharmaceuticals within the context of cold boxes used in the theatre environment. A literature search could not identify any published articles internationally or nationally pertaining to the use of cold boxes for the storage of heat-sensitive pharmaceuticals. Thus anaesthetists, although uniquely positioned at the end of the cold chain, represent a crucial link in the maintenance of the cold chain.

2. Problem statement

The US Pharmacopeia’s Medmarx® medication-error reporting system has reported nearly 1000 incidences involving errors associated with refrigerated medications, many of which attributable to the inappropriate storage of medications (5).

Anaesthetists assume responsibility for the administration of pharmaceuticals to their patients in the peri-operative period and consequently the inherent complications associated with all iatrogenic reactions, both benign and malignant. This is in accordance with the Medicines and Related Substances Act sections 36 and 37 (37).

Many of the pharmaceuticals used in theatre for anaesthesia are refrigerated. Degradation of these heat-sensitive products is dependent on numerous factors such as: temperature concentration of reactants, pH, catalysts, etc (38). Thus their removal from the refrigerator and storage within cold boxes represents a potential break in the cold chain. A study conducted by Gammon et al.(33), showed accelerated decreases in concentrations of succinylcholine especially when exposed to temperature excursions above label recommendations. Thus failure to maintain the cold chain within the cold boxes not only poses a financial burden, as a result of increased drug utilisation due to loss of drug potency, but also carries with it potentially catastrophic effects for patients

in the form of iatrogenically induced effects. Continuity of the cold chain and maintaining the integrity of heat-sensitive pharmaceuticals is therefore the inherent responsibility of every anaesthetist.

International and national guidelines are available (3, 34), detailing specific requirements for the transportation and storage of heat-sensitive biological vaccines, however there is a paucity of information pertaining to heat-sensitive pharmaceuticals stored in cold boxes within theatre. Similarly recommendations from manufacturers, detailing general storage requirements, do not detail the specific issues of heat cycling, temperature excursions and freeze-thawing of heat-sensitive pharmaceuticals.

Little is known with regard to the adequacy of the cold chain and the potentially damaging environment that heat-sensitive pharmaceuticals may be exposed to within cold boxes in the operating theatres at Chris Hani Baragwanath Academic Hospital (CHBAH).

3. Aims

This study will be done in two parts.

The aim of the first part of the study is to describe the adequacy of the cold chain used for the storage of heat-sensitive pharmaceuticals in the Department of Anaesthesiology at CHBAH.

The aim of the second part of the study is to quantify the thermal performance of the various types of cold boxes used in the Department of Anaesthesiology, using newly purchased cold boxes and cold packs.

4. Objectives

The objectives of Part 1 of the study are to:

- describe the refrigerator used for storage of heat-sensitive pharmaceuticals and ambient air temperatures measured within the refrigerator over one working day
- describe the cold boxes with regards to type, dimensions and condition
- describe the cold packs/cool packs used and their preparation
- describe the manner in which cold boxes are packed
- describe whether temperature monitoring devices were employed for monitoring temperature within the cold boxes
- describe the ambient air temperatures measured within cold boxes.

The objectives of Part 2 of the study are to:

- measure the ambient air temperature of fabric cold boxes with 1, 2, 3 and 4 cold packs in situ for seven consecutive days between 08:00 and 16:00
- measure the ambient air temperature of polystyrene cold boxes with 1, 2, 3 and 4 cold packs in situ for seven consecutive days between 08:00 and 16:00
- measure the ambient air temperature of hard plastic cold boxes with 1, 2, 3 and 4 cold packs in situ for seven consecutive days between 08:00 and 16:00
- compare the thermal performance of the various types of cold boxes and the effect of the number of cold packs in situ.

5. Research assumptions

The following definitions will be used in this study.

Cold chain: a system consisting of people, equipment and heat-sensitive pharmaceuticals which ensure the temperature is maintained within a specified temperature range from the time of production through to the administration thereof. In this study the cold chain is from the refrigerator in the Department of Anaesthesiology to the administration of the medication from the cold boxes in theatre.

Cold life: the moment when the container lid is closed until the temperature of the warmest point in the vaccine storage compartment first reaches +10°C, at a constant ambient temperature of +43°C.

Mean kinetic temperature: the single calculated temperature, at which the total amount of degradation over a particular period, is equal to the sum of the individual degradations that would occur at various temperatures.

Cold box: for the purpose of this study, “cold box” refers to storage containers used in the theatres for the storage of heat-sensitive pharmaceuticals. The commercially available cold boxes used at CHBAH are either: fabric, polystyrene or hard plastic. These cold boxes do not conform to medically validated criteria for storage of heat-sensitive pharmaceuticals.

Cold pack: a water-pack frozen to a temperature between -5°C and -20°C before use.

Cool pack: a gel pack pre-cooled to a temperature between +2°C to +8°C before use.

Correctly packed cold box: refers to a cold box containing correctly prepared cold packs that are initially frozen at -5°C to -20°C, allowed to precipitate out of the freezer, wrapped in bubble wrap and subsequently placed into the cold box. Heat-sensitive pharmaceuticals still in their original packaging are then placed on top of/next to the prepared cold packs with a data logger thermometer (DLT) placed in the central drug compartment. A further bubble wrapped cold pack should then be placed on top of the central drug compartment to seal it and the lid of the cold box closed.

Data logger thermometers (DLT): for the purpose of this study DLT refers to scientifically validated and calibrated thermometers used for continuous logging of temperatures. MAJORTECH® MT643 K-type temperature data loggers were used. These DLTs have a temperature range of -200°C to +1370°C with an accuracy of ±1°C.

Garage – this is term used to describe the area at CHBAH where the refrigerator containing cold/cool packs and heat-sensitive pharmaceuticals are kept.

Weekday – will be Monday to Friday from 08:00 to 16:00.

6. Demarcation of the study field

This study will be conducted within all theatres at CHBAH.

CHBAH is a central hospital located in Soweto, Gauteng and serves as a referral centre for smaller peripheral hospitals and clinics from the surrounding area. The theatre complex at CHBAH consists of 23 theatres of which six are emergency theatres functioning 24 hours a day and the remaining 17 theatres accommodating the various elective surgical subspecialties.

CHBAH is affiliated to the University of the Witwatersrand.

7. Ethical considerations

Approval to conduct this study will be obtained from the Graduate Studies Committee of Wits. An ethics waver (Appendix A) will be applied for from the Human Research Ethics Committee (Medical) of Wits as this is an equipment based study. Approval to conduct the study will further be obtained from the Medical Advisor Committee of the CHBAH (Appendices B). The Matron in charge of the various theatre complexes will be informed of the study.

No theatre staff will be implicated in the study as only the equipment will be evaluated. If the equipment involved in the maintenance of the cold chain is found to be inadequate, the Head of Department of Anaesthesiology will be notified accordingly. This study does not involve any drug or therapeutic management and will be conducted by adhering to the South African Good Clinical Research Practice Guidelines (39) and the Declaration of Helsinki (40) . All data captured will be stored securely in a locked cupboard for a period of six years.

8. Research methodology

8.1 Study design

The research design is that of a descriptive, prospective and contextual study.

A descriptive study is said to define the characteristics of the sample under investigation with the researcher playing no part in the manipulation of any of the variables (41). This study will make use of DLTs to describe and quantify the adequacy of the cold chain and thermal performance of the cold boxes within theatres of CHBAH.

A prospective study measures population variables which are recorded over a period of time (41). Hence by taking the physical measurements of ambient air temperatures within the refrigerator and cold boxes the variables within this study fulfil the criteria of a prospective study.

This study is contextual as it takes place within the specific location of CHBAH theatres (42).

8.2 Study population

The study population for Part 1 will be the refrigerator, cold boxes and cold/cool packs used in theatre.

The study population for Part 2 will be the newly purchased cold boxes and cold packs for the purpose of assessing cold box thermal performance.

8.3 Study sample

Sample size

No studies have been identified internationally or nationally on the use of cold boxes for the storage of heat-sensitive pharmaceuticals within theatre to guide sample size determination.

The sample size for Part 1 will consist of the refrigerator and all 23 cold boxes and their associated cold/cool packs. The reason for using the total cold box population is that the thermal performance of cold boxes varies amongst the different types of boxes used in theatre and is dependent on numerous extraneous factors i.e. type of box and condition, cold/cool packs used, packing method employed, etc. It would therefore be difficult to extrapolate findings from a smaller sample group.

The sample size for Part 2 will consist of 12 boxes (four of each of the three types: fabric, polystyrene and hard plastic), and 30 cold packs. This will be done over a seven day period which will give a total of 84 temperature recordings.

Sampling method

It is the intention of this study to assess all of the elements of the cold chain in theatre at CHBAH and thus sampling is purposive. In purposive sampling the researcher specifically selects certain participants, elements, events or incidents, due their importance (43). The risk of precision of judgement of researcher on inclusion criteria is a concern in this type of sampling method (44). However as all the cold boxes will be included in the study, the only inclusion criterion is the cold box and as such no judgement is required and additively no exclusion criterion exists.

8.4 Data collection

Part 1 of data collection

All cold boxes used in theatre for the storage of heat-sensitive pharmaceuticals are prepared by each theatres respective registrar before the commencement of the list. This normally occurs at approximately 07:30 in the morning with registrars collecting drug boxes, cold/cool packs and heat-sensitive pharmaceuticals from the refrigerator in theatre.

Thus for the purpose of this study all cold boxes will be collected before commencement of theatre and each given a unique number for reference and identification purposes. The cold boxes will then be described in terms of their defining characteristics. The subsequent findings will be captured on a data collection sheet (Appendix 3).

DLTs will be secured in each of the cold boxes on the bottom centre of the cold box before the addition of cold/cool packs and drugs (likely coldest point in the cold box) at approximately 07:00. Additively a DLT will be placed in the refrigerator used for the storage of heat-sensitive pharmaceuticals and cold packs in theatre. The DLTs will remain in the cold boxes and refrigerator until the completion of the theatre day, concluding 16:00 when they will be collected. Data from all DLTs will be subsequently downloaded and analysed at a later date. Simultaneously after collection of the temperature probes, a description of the number of cold packs as well as the manner in which the cold boxes were packed will be added to data collection sheet.

The data collection sheet (Appendix 3) will be devised to record the data:

- refrigerator type and temperature
- theatre ambient air temperature
- type of cold box (fabric, polystyrene, hard plastic)
- physical appearance/condition
- dimensions (length x width x height and litre)
- cold box ambient air temperature
- type of cold/cool pack
- number of cold packs placed in situ and packing method employed

Photographic evidence of each of the cold boxes will be taken before each inspection, attached to the data collection sheet and included in an appendix of the final report.

The data will be collected personally by the researcher and entered into a Microsoft Excel spreadsheet 2013.

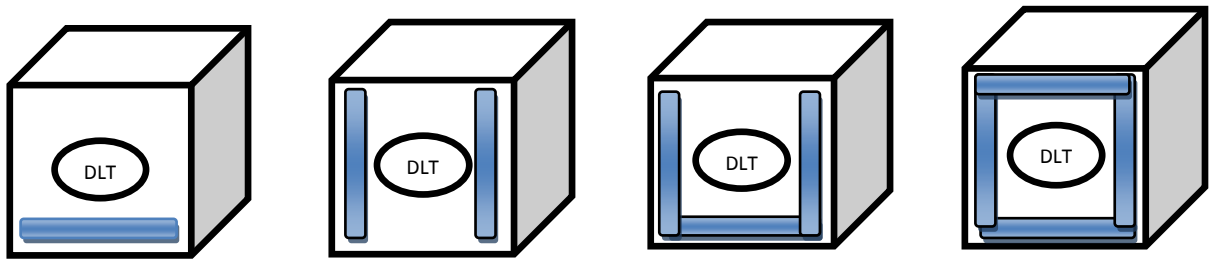
Part 2 of data collection

A total of 12 cold boxes and 30 cold packs will be used for Part 2 of the study. Four of each type of cold box (fabric, polystyrene and hard plastic) will be available. In each of

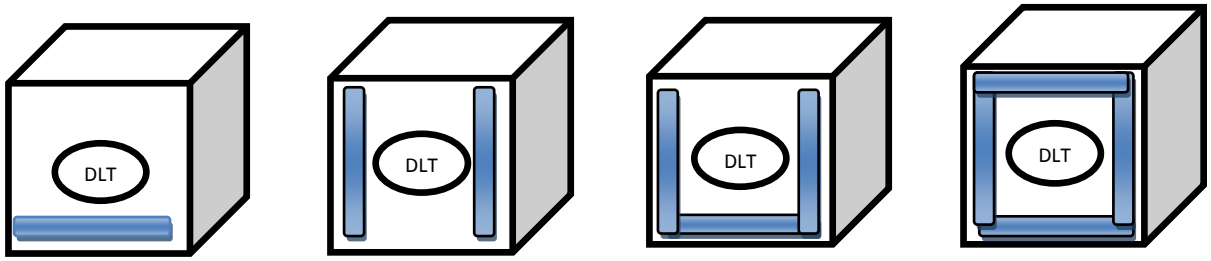
the same type of cold boxes 1, 2, 3 and 4 cold packs and a DLT will be placed in the bottom centre of the cold box and the lid closed. The ambient air temperature in each of the 12 cold boxes will be measured from 08:00 to 16:00 at a constant room temperature of +25°C (Diagram 1). Temperatures within the 12 boxes will be measured over a seven day consecutive period resulting in a total of 84 samples (n = 24) collected.

Diagram 1. Four samples of each type of cold box (fabric, polystyrene and hard plastic) with cold packs and DLT in situ

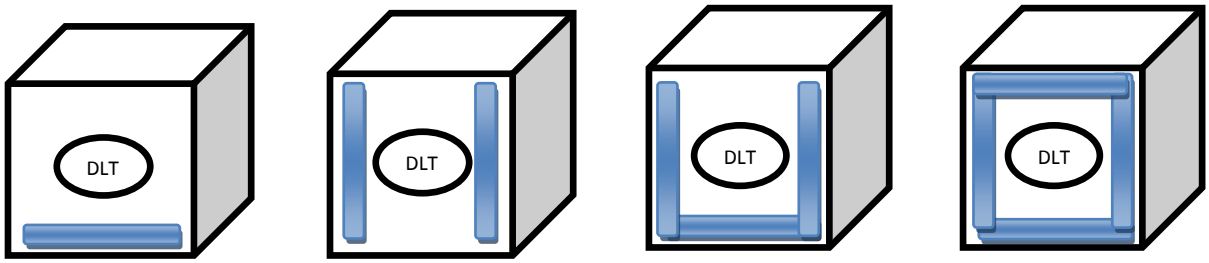
Fabric cold boxes



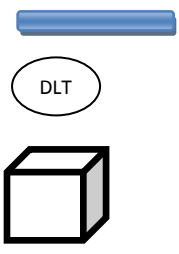
Polystyrene cold boxes



Hard plastic cold boxes



Key:



Cold pack

Data logger temperature

Cold box

8.5 Statistical analysis

All data collected will be analysed in consultation with a biostatistician using GraphPad Prism 7, statistical program. Descriptive and inferential statistics will be used to analyse the data. Categorical variables will be described using frequencies and percentages. Continuous variables will be described using means and standard deviations or medians and interquartile ranges depending on the distribution of the data. In Part 2 of the study, ANOVA will be used to compare thermal performance of the cold boxes and their cold packs. A p value of <0.05 will be considered statistically significant.

9. Significance of the study

An extensive literature search has been conducted on the use of cold boxes in theatre for the maintenance heat-sensitive pharmaceuticals, and as yet, no studies internationally or nationally have been identified. The USP Medmarx® medication-error reporting system has reported nearly 1000 incidences involving errors associated with refrigerated medications, many of which attributable are to inappropriate storage of medications (5).

It has been documented that temperature has a significant effect on the stability of pharmaceutical products (14). However pharmaceutical manufacturers are not required to report at what temperatures their products are stable, but are required only to manufacture products stable within the environments dictated by their package labelling (26). Studies conducted within the emergency medical services pre-hospital environment have provided some insight into the aforementioned effects of temperature excursions of heat-sensitive pharmaceuticals beyond recommended storage conditions within cold boxes.

The maintenance of the cold chain within cold boxes used at CHBAH for the storage of heat-sensitive pharmaceuticals is not currently known and as such necessitates investigation. If the cold chain is found to be inadequate this may lead to a change in practice and consequently decreased cost to the hospital and improved patient safety.

10. Validity and reliability of the study

The validity of a study refers to the degree to which a measurement represents a true value and is always a matter of degree and is never absolute. It allows the conclusion of a study to be justified based on its design and interpretation (44).

Reliability of a study refers to the consistency and repeatability with which an instrument measures variables and the extent to which random errors may occur in the measurement (41).

The validity and reliability of this study will be ensured by:

- the use of an appropriate study design and data gathering techniques
- data collection by a single researcher, therefore ensuring consistency of data collection
- adhering to guidelines set out by the World Health Organisation (WHO) with regards to the specifications of vaccine cold box thermal performance, as well as the South African national Department of Health guidelines on cold chain and immunization operations manual for vaccines and heat-sensitive pharmaceuticals (3, 34).
- the sample size being equal to the population size and therefore no sampling bias
- DLTs are scientifically validated for temperature data logging and calibrated prior to use.

11. Potential limitations of the study

Limitations can be defined as restrictions or problems that decrease the ability to generalise the findings of a study and can be either theoretical or methodological in nature (43).

Although the study population will be all the cold boxes at CHBAH (total of 23), this study will have contextual limitations in that it is confined to a single setting. This may limit generalising of the findings to other theatre environments.

12. Project outline time frame

Table 1 Proposed time frame for the study

	2014										2015	
	Jan	Feb	Mar	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Jan	Feb
Chapter 1 - 3												
Proposal												
Ethics committee submission												
Postgraduate committee submission												
Data Collection												
Data Analysis												
Chapter 4 & 5												
Discussion with supervisors												
Edit final draft												
Submit												

13. Funding

Funding of all paper and printing costs incurred during the study will be covered by the author. Validated DLTs will be purchased with funds obtained from Department of Anaesthesiology at Wits

Equipment for Part 2 of the study will be donated by pharmaceutical companies.

The proposed budget for this study is illustrated in Table 2.

Table 2 Budget for the study

Description	Price per item	Amount of items	Total
Printing Proposal	60c per page	±400	R240.00
Printing data collection sheets	60c per page	±50	R30.00
Printing research report	60c per page	±1000	R600.00
Binding of final research report	R150	3	R450.00
			R1320.00

Appendix 1: Letter to the Ethics Committee

Dr Graham Anthony Boy

Department of Anaesthesiology

University of the Witwatersrand

27-02-2014

ATT: Professor Peter Cleaton-Jones

Chair: Human Ethics Research Committee

Re: ADEQUACY OF THE COLD CHAIN USED FOR THE STORAGE OF HEAT-SENSITIVE PHARMACEUTICALS IN A DEPARTMENT OF ANAESTHESIOLOGY

Dear Prof. Cleaton-Jones

I am a registrar in the Department of Anaesthesiology. My research component of my M Med is a non-human study proposed to assess the thermal performance of cold chain used for the storage of heat-sensitive pharmaceuticals in Chris Hani Baragwanath Academic Hospital theatres.

The cold boxes and refrigerator ambient air temperatures will be assessed by using validated data logger temperature (DLTs) probes. I would like to request an ethics waiver for this study.

Yours sincerely

Dr Graham Anthony Boy

boy.graham@gmail.com

Cell no: 0722396934

Appendix 2: Letters to the Medical Advisory Committee Chris Hani Baragwanath Academic Hospital

Dr Graham Boy

Department of Anaesthesiology

University of the Witwatersrand

27-02-2014

To whom it may concern

Re: Permission to conduct research at Chris Hani Baragwanath Academic Hospital

I am a currently a registrar in the Department of Anaesthesiology conducting non-human research for the purpose of my M Med entitled: **ADEQUACY OF THE COLD CHAIN USED FOR THE STORAGE OF HEAT-SENSITIVE PHARMACEUTICALS IN A DEPARTMENT OF ANAESTHESIOLOGY**. I aim to conduct the study at the Chris Hani Baragwanath Academic Hospital.

The study will be a descriptive, prospective, contextual study assessing the adequacy of the cold chain used for the storage of heat-sensitive pharmaceuticals in operating theatres. The hospital will not be held financially liable for any costs incurred during this research and the results will be available for your perusal should you wish to review them.

Please find attached copies of my proposal, approval to conduct the study from the Postgraduate Committee and my ethics waiver. Thank you for your consideration.

Yours sincerely,

Dr Graham Anthony Boy

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Appendix 3: Part 1 Data Collection Sheet:

Theatre sample no	Type of cold box used	Cold box dimensions cm (length x width x height)	Volume in litres	Condition of cold box	Open or closed cold box	Type of cold/cool pack used	No of packs inside cold box	Manner in which cold box packed
1								
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
13								
14								
15								
16								
17								
18								
19								

Appendix 4: Part 2 Data Collection Sheet:

	Ambient Air Temperature Experienced in Cold Box over period 08:00 – 16:00 with:			
	1 Cold Pack in situ	2 Cold Packs in situ	3 Cold Packs in situ	4 Cold Packs in situ
Fabric cold box				
Polystyrene cold box				
Hard plastic cold box				

SECTION SIX - REFERENCES

1. Stelfox H, Palmisani S, Scurlock C, Orav EJ, Bates D. The "To Err is Human" report and the patient safety literature. Qual Saf Health Care. 2006;15:174 - 8.
2. WHO. Pharmacovigelence Guidelines [12 January 2014]. Available from: http://www.who.int/medicines/areas/quality_safety/safety_efficacy/S.AfricaDraftGuidelines.pdf.
3. Department of Health. Cold Chain and Immunisation Operations Manual: Guidelines for Handling Heat Sensitive Vaccines and Pharmaceuticals. South Africa.2015. Available from: http://www.health.gov.za/index.php/2014-08-15-12-53-24?download=2573:cold-chain-and-immunisation-operations-manual.
4. Ammann C. Stability studies needed to define the handling and transport conditions of sensitive pharmaceutical or biotechnical products. AAPS J. 2011;12(4):1264 - 75.
5. Santell J, Hicks R, McMeekin J, Cousins D. Medication errors: Experience of the United States Pharmacopeia (USP) MEDMARX Reporting System. J Clin Pharmacol. 2003;43(7):760 - 7.
6. Gordon P. Wrong drug administration errors amongst anaesthetists in a South African teaching hospital. SAJAA. May 2004:7 - 8.
7. WHO. Good distribution practices for pharmaceutical products. Technical Report Series. 2010;No 957(Annex 5).
8. Stability testing of new drug substances and products - Q1A (R2) International Conference on Harmonization.; 6 February 2003. Available from: http://www.ich.org/products/guidelines/quality/quality-single/article/stability-testing-of-new-drug-substances-and-products.html.
9. PDA. Technical Report no. 39: Cold chain guidance for medicinal products: maintaining the quality of temperature-sensitive medicinal products through the transportation environment. Originally published 2005, revised 2007. Available from: https://www.pda.org/publications/pda-publications/pda-technical-reports.
10. PDA. Technical Report no. 46: Last Mile: guidance for the good distribution practices for pharmaceutical products to the end user. 2009. Available from: https://www.pda.org/publications/pda-publications/pda-technical-reports.
11. US Pharmacopoeia - National Formulary [USP 39 NF 34]. Rockville, Md.2016.
12. Ziance R, Chandler C, Bishara R. Integration of temperature-controlled requirements into pharmacy practice. J Am Pharm Assoc. 2009;49(3):61 - 9.
13. Rubiana F, Wanderley P. Storage conditions for stability testing of pharmaceuticals in hot and humid regions. Drug Dev Ind Pharm. 2007;33:393 - 401.
14. Kommanaboyina B, Rhodes C. Trends in stability testing, with emphasis on stability during distribution and storage. Drug Dev Ind Pharm. 1999;25(7):857 - 68.
15. Florence A, Attwood D. Estabilidade de drogas. In Principios Fisicos Quimicos em Farmacia. 2003:155 - 218. Portuguese.
16. Haynes JD. Worldwide virtual temperatures for product stability testing. J Pharm Sci. 1971;60:927 - 9.
17. Grimm W. Storage conditions for stability testing in the EC, Japan and USA; the most important market for drug products. Drug Dev Ind Pharm. 1993;19:2795 - 830.
18. Kishore A, Nagwekar J. Influence of temperature and hydrophobic group-assocaited icebergs on the activation energy of drug decompostionand its implication in drug shelf-life prediction. Pharm Res. 1990;7:730 - 5.
19. Seevers R, Ulrich D, Bishara R. The use of mean kinetic temperature (MKT) in the handling, storage, and distribution of temperature sensitive pharmaceuticals. Pharmaceutical Outsourcing: Cold Chain. 2009:12 - 6.

20. Emmons S, Abeyewardene L, Ramakrishan U. Case of frozen thiopental. Anesth Analg. 1998;87:748.
21. Stone J, Fawcett W. A case of frozen succinylcholine encountered. Anesth Analg. 2002;95:1465.
22. Kumarvel V. Frozen succinylcholine. Anaesthesia. 2006;61:190 - 202.
23. Kupper T, Schraut B, Rieke B, Hemmerling AV, Schoffl V, Steffgen J. Drugs and drug administration in extreme environments. J Travel Med. 2006;13:35 - 47.
24. Vaisala. Mean Kinetic Temperature in GxP Environments/Definitions and Applications [Application note]. 2016 [24 January 2017]. Available from: www.vaisala.com/requestinfo.
25. Nirmal K, Ajeya J. Temperature excursion management: A novel approach of quality system in pharmaceutical industry. Saudi Pharm J. 2016.
26. Brown LH, Krumperman K, Fullager J. Out-of-hospital medication storage temperatures: A review of literature and directions for the future. Prehosp Emerg Care. 2004;8:200 - 7.
27. Colin JN, Singlas E. Metabolism and pharmacokinetics of atracurium. Ann Fr Anesth Reanim. 1985;4:465 - 70.
28. Stiller RL, Cook DR, Chakravorti S. In vitro degradation of atracurium in human plasma. Br J Anaesth. 1985;57:1085 - 8.
29. Valenzuela TD, Criss EA, Hammargren WM, Schram KH, Spaite DW, Meislin HW, et al. Thermal stability of prehospital medications. Ann Emerg Med. 1989;18:173 - 6.
30. DuBois W. Drug storage temperatures in rescue vehicles. J Emerg Med. 1999;18:345 - 8.
31. Allegra JR, Brennan J, Lanier V, Lavery R, Mackenzie B. Storage temperatures of out-of-hospital medications. Acad Emerg Med. 1999;6:1098 - 103.
32. Church WH, Hu SS, Henry A. Thermal degredation of injectable epinephrine. Am J Emerg Med. 1994;12:306 - 9.
33. Gammon DL, Su S, Jordan J, Patterson R, Finley PJ, Lowe C, et al. Alteration in prehospital drug concentration after thermal exposure. Am J Emerg Med. 2007;26:566 - 73.
34. World Health Organisation. PQS performance specification. Vaccine Cold Box 2010 [2014]. Available from: http://www.who.int/immunization_standards/vaccine_quality/pqs_e004_cb01_2_pps.pdf.
35. McColloster P, Vallbona C. Graphic-output temperature data loggers for monitoring vaccine refrigeration: Implications for pertussis. Am J Pub Health. 2011;101(1):46 - 7.
36. I.M.S. Institute for Healthcare Informatics. The Global Use of Medicines: Outlook Through 2016. 2012. Available from: http://www.imshealth.com/deployedfiles/ims/Global/Content/Insights/IMS%20Institute%20for%20Healthcare%20Informatics/Global%20Use%20of%20Meds%202011/Medicines_Outlook_Through_2016_Report.pdf.
37. Department of Health. GENERAL REGULATIONS MADE IN TERMS OF THE MEDICINES AND RELATED SUBSTANCES ACT, 1965(ACT NO. 101 OF 1965), AS AMENDED 15 November 2015 [Accessed 2014]. Available from: http://www.mccza.com/genericDocuments/Regulations_to_Act_101_published_2003.pdf.
38. Orser B.A. Chen R.J. Yee D.A. Medication Errors in Anaesthetic Practice: A survey of 687 practitioners. Canadian Journal of Anaesthetics. 2001;48:139 - 46.
39. Guidelines for Good Practice in the Conduct of Clinical Trials with Human Participants in South Africa: Department of Health: Pretoria, South Africa; 2006 [2014]. Available from: http://research.ukzn.ac.za/Libraries/Notices2011/SA_GCP_2006_sflb.sflb.ashx.
40. 59th World Medical Association General Assembly. Decleration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects. 2008 [cited 2014]. Available from: http://www.wma.net/en/30publications/10policies/b3/17c.pdf.
41. Brink H. Van der Walt C. Van Rensburg G. Fundamentals in Research Methodology fo Healthcare Professionals. Second ed. Cape Town: Juta & Company Ltd; 2012.
42. Burns N, Grove S. Understanding qualitative research design. 6 ed. Henderson L, editor. Missouri, USA: Saunders Elsiever; 2009.
43. Burns N. Grove S. The Practice of Nursing Research: Appraisal, Synthesis, and Generation of Evidence. Sixth ed2009.

44. Botma Y. Greef M. Mulaudzi F.M. Wright S.C.D. Research in Health Sciences.: Pearson Education; 2009.