

# All You Need To Know About Temperature Storage Control



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# WHY?



The Logic Behind the Requirement



# The Logic Behind the Requirement



- Pharmaceuticals degrade over time
- Degradation can be accelerated by “extreme” storage conditions – both hot and cold
- At best, degradation can lead to lack of effect (pharmaceutical loses it’s potency)
- At worst, degradation can be dangerous (toxic breakdown products, precipitation of solid substances from solution for injection)

# The Logic Behind the Requirement

- Clinical trials involve the testing of investigational medicinal products (new ingredients or new delivery methods)
- Knowledge on the potency and toxicity of the investigational medicinal product is incomplete
- During the conduct of the trial, new data collected will “fill-out” the picture we have of the investigational medicinal product and storage requirements may change and become more or less strict

# The Logic Behind the Requirement

There are 2 risks involved in using drug that has been stored incorrectly:

- Risk to the patient due to unexpected degradation - toxic or ineffective IMP
- Risk of IMP being incorrectly considered “ineffective” or “too toxic” for further development (trial does not reach it’s safety or efficacy endpoint)

# WHY?



## What Do The Guidelines Say?

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## ICH GCP 4.6.4:

- “the investigational product(s) should be stored as specified by the sponsor and in accordance with applicable regulatory requirements
- 5.13.2; The sponsor should determine, for the investigational product(s), acceptable storage temperatures, storage conditions (e.g. protection from light), storage times, reconstitution fluids and procedures, and devices for product infusion, if any. The sponsor should inform all involved parties (e.g. monitors, investigators, pharmacists, storage managers) of these determinations.
- 5.18.4 “Monitor’s responsibilities – verifying for the investigational product(s): That storage times and conditions are acceptable ....”

# What Do The Guidelines Say?

## **SA GCP 3.6:**

- The investigational product(s) should be stored as specified by the sponsor, and in line with Good Pharmacy Practice (GPP) in South Africa, and the regulatory authority regulations and conditions.
- The sponsor should determine, for the investigational product(s), acceptable storage temperatures, storage conditions (e.g. protection from light), storage times, reconstitution fluids and procedures, and devices for product infusion, if any. Compliance with the GPP, where applicable, will be required. The sponsor should inform all involved parties (e.g. monitors, investigators, pharmacists, storage managers) of these determinations.
- The monitor should also: ...check that storage, dispensing and documentation of the supply of investigational product(s) is safe and appropriate and in accordance with local regulations and SOPs;

# What Do The Guidelines Say?

- **SA Good Manufacturing Practice (Mar09 v4):** “The application of GMP to the manufacture of investigational medicinal products is intended to ensure that trial subjects are not placed at risk, and that the results of clinical trials are unaffected by inadequate safety, quality or efficacy arising from unsatisfactory manufacture.”
- **SA Good Pharmacy Practice:** no specific guidance on the storage of trial medication however “ensure that optimal storage conditions are monitored”; “temperature must be below 25 deg C”; “refrigerator capable of storing products at temperatures between 2 and 8 deg C”

# HOW?



The Pros and Cons of the Devices

# The Pros and Cons of the Devices

## The “Ideal” Temperature Monitoring Device

- Continuous recording of temperature experienced in the room / fridge / freezer
- Does not rely on the physical presence of a person to record temperature
- Record is accurate, easily read and interpreted, and cannot be altered
- “Alarm” is triggered when temperature goes out of pre-specified range

# The Pros and Cons of the Devices

## Datalogger – linked to a remote alarm – Pros

(phonecall or SMS to responsible person / people)

- Temperature is recorded on evenings, weekends and holidays
- Instant notification of a problem – chance to take corrective and preventative action

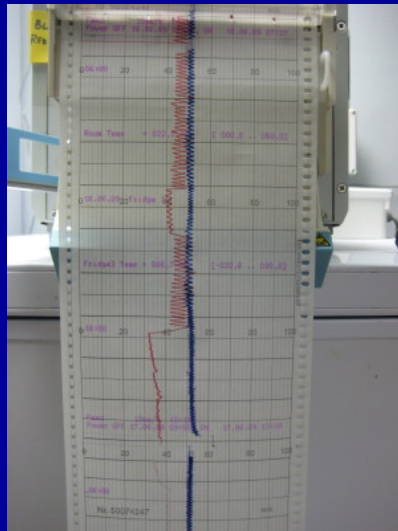


# The Pros and Cons of the Devices

## Datalogger – linked to a remote alarm – Cons

- Expensive to purchase and install
- Makes you lazy – still need to review and sign off temperature records regularly (weekly) and check for power problems
- Remember to download data / make backups (automatic overwriting of data by electronic systems)
- Still relies on phone network to send out an alarm

# How Does A Datalogger Work?



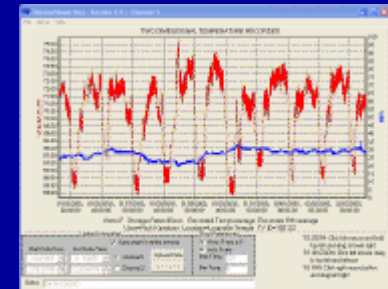
Microsoft Excel - sample

File Edit View Insert Format Tools Data Window Help

Anal

1 -Date Format: mm/dd/yyyy hh:mm:ss  
2 -File Created On: 10/12/2006 15:44:45  
3 -User Name: Rick Krastner  
4 -User Location: Lemphr 2  
5 -T410 Thermistor only  
6 -PC Software Version: Thermo/connected - Version 4.2

Date/Time	Celcius	Kelvin	Fahrenheit	RH
10/1/2004 14:10	22.7842	296.9342	73.0116	49
10/1/2004 14:20	22.9842	296.7342	72.9916	49
10/1/2004 14:30	22.4809	295.6309	72.4716	50
10/1/2004 14:40	22.3609	295.5099	72.2316	50
10/1/2004 14:50	22.2176	295.3676	71.9916	50
10/1/2004 15:00	22.1909	295.3009	71.8716	51
10/1/2004 15:10	22.0842	295.2542	71.7516	51
10/1/2004 15:20	22.0809	295.2009	71.6916	51
10/1/2004 15:30	22.0176	295.1676	71.6316	51
10/1/2004 15:40	22.0176	295.1676	71.6316	51
10/1/2004 15:50	22.0171	295.1671	71.6307	51
10/1/2004 16:00	21.9804	295.1004	71.5107	51
10/1/2004 16:10	21.9171	295.0671	71.4507	51
10/1/2004 16:20	21.8837	295.0337	71.3907	51
10/1/2004 16:30	21.8837	295.0337	71.3907	51
10/1/2004 16:40	22.2176	295.3676	71.9916	51
10/1/2004 16:50	21.9842	295.1342	71.5716	52
10/1/2004 17:00	21.9804	295.1004	71.5107	52
10/1/2004 17:10	21.8837	295.0337	71.3907	52
10/1/2004 17:20	21.8604	295.0004	71.3307	52
10/1/2004 17:30	21.9171	295.1671	71.2707	52
10/1/2004 17:40	21.7504	294.9004	71.1507	52
10/1/2004 17:50	21.7504	294.9004	71.1507	52
10/1/2004 18:00	21.6837	294.8337	71.0307	52
10/1/2004 18:10	22.0171	295.1671	71.6307	52



# The “Other” Temperature Monitoring Devices vs the “Ideal”

Datalogger  
with noise /  
visual / no  
alarm



Mercury  
min-max  
thermometer



Digital min-  
max  
thermometer



Alcohol /  
mercury  
thermometer  
or bi-metal  
dial  
thermometer



Continuous recording of temperature	☺	☺ / X	☺ / X	X
Does not rely on the physical presence of a person to record temperature	☺	X	X	X
Record is accurate, easily read and interpreted, and cannot be altered	☺	X	X	X
“Alarm” is triggered when temperature goes out of pre-specified range	☺ / X	X	X	X

## The “Other” Temperature Monitoring Devices

<b>Device</b>	<b>It can</b>	<b>It can't</b>
<b>Datalogger with noise / visual / no alarm</b>	Quantitatively identify out of range temperature and time of exposure	Notify you immediately of out-of-range temperature (unless you're near the device)
<b>Mercury min-max thermometer</b>	Quantitatively identify out of range temperature	Notify you immediately of out-of-range temperature
<b>Digital min-max thermometer</b>		Time of out-of-range exposure can only be estimated, assuming it occurred directly after last reading
<b>Alcohol / mercury thermometer or bi-metal dial thermometer</b>	Identify current temperature – need to read at start and end of day to get approximation of min and max	

## The “Other” Temperature Monitoring Devices

Device	Pros	Cons
<b>Datalogger with noise / visual / no alarm</b>	Good data available when out-of-range exposures occur	Same as logger with remote alarm
<b>Mercury min-max thermometer</b>	Cheap	Can be difficult to read, especially for fridge temperatures
<b>Digital min-max thermometer</b>	Cheap 2 probe versions allow for room and fridge monitoring by 1 device	Readings from 2 probe versions can be confusing if both are in same location
<b>Alcohol / mercury thermometer or bi-metal dial thermometer</b>	Cheap	Relies on regular reading at correct times to detect problems

# How Does A Mercury Min-Max Thermometer Work?

- The mercury measures the current temperature (both sides should be the same)
- Read min and max from the bottom of the “sticks”
- Red = negative, Black = positive (like accounts)
- Pressing the “reset” button lets the sticks slide back down to the top of the mercury



# How Does A Digital Min-Max Thermometer Work?

- BEWARE – most of these devices have TWO probes (an IN and an OUT probe)
- If you aren't using both probes, make sure you use the same one, and document which one you are using
- Each probe has it's own MIN and MAX reading
- Lots of buttons can lead to lots of confusion



# How Does An Alcohol / Mercury or Bi-metal Thermometer Work?

- The current temperature shows on the dial.
- Needs to be read first and last thing to be of any use



# WHEN?



Which device for which application?

# Which device for which application?

## Datalogger – linked to a remote alarm

- Very temperature sensitive products – known stability problems
- Good choice when working with refrigerated or frozen IMP
- Good choice for large / dedicated trial units with financial resources



# Which device for which application?

## Datalogger with noise / visual / no alarm

- Good choice when working with refrigerated or frozen IMP
- “Mobile” versions available for use during IMP transportation
- If you’ve gone this far, you might as well connect it to the phone as well



# Which device for which application?

## Digital min-max thermometer

- Option for small research unit, especially when monitoring stable refrigerated IMP and room temperature IMP with the same device
- Need “aware” personnel reading and recording temperatures (need to read regularly, daily is best, and reset device after each reading)



# Which device for which application?

## Mercury min-max thermometer

- Option for small research unit, especially when only monitoring room temperature IMP
- Need “aware” personnel reading and recording temperatures (need to read regularly, daily is best, and reset device after each reading)



# Which device for which application?

## Alcohol / mercury thermometer or bi-metal dial thermometer



SA Good Pharmacy Practice says this device and NOT a min-max should be used in a refrigerator for registered drugs

- It should be hung from the middle shelf of the refrigerator
- Read twice a day, first thing in the morning, and at the end of the day

# I Have a Device, Now What?



Temperature Monitoring Doesn't  
End With The Thermometer

# I Have a Device, Now What?

**A key part of the process is validation – are you sure your equipment works properly?**

- Has your thermometer been calibrated recently (ever)?
  - Calibration is far more expensive than the price of the device
  - Cheap devices cannot be adjusted so “calibration” is really just “accuracy determination”
  - Multi-point calibration needed



# I Have a Device, Now What?

**A key part of the process is validation – are you sure your equipment works properly?**

- Is your air-conditioner working?
- Does it stay on when you aren't there?
- Is it serviced regularly?
- What happens during a power failure?

# I Have a Device, Now What?

**A key part of the process is validation – are you sure your equipment works properly?**

- Does your fridge work properly?
- Is it packed properly?
- What happens during a power failure?
- Are you defrosting it regularly?
- What are you doing with the IMP when you defrost the fridge?
- Do you know where the hot and cold spots are?

# Good Fridge Packing

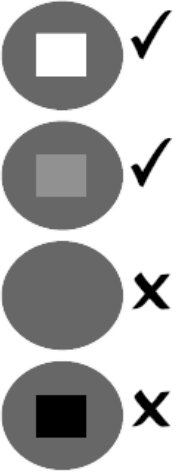


# Transporting IMP

- Various cold chain monitors exist, and like the “fixed” devices they have their pros and cons
  - Dataloggers (paper or electronic) are the most common (Temptale 4 range)
  - Some only give a Yes / No sign, but can be downloaded later (Temptale 3)
  - Choosing your device depends on your drug

# Transporting IMP

Simple devices used for vaccines may be suitable for some IMP too




Inner square lighter than outer ring.  
If the expiry date has not been passed,  
**USE** the vaccine.

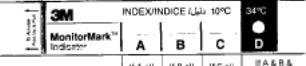
At a later time:  
Inner square still lighter than outer ring.  
If the expiry date has not been passed,  
**USE** the vaccine.

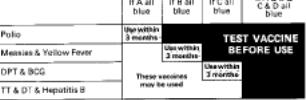
**Discard point:**  
Inner square matches colour of outer ring.  
**DO NOT** use the vaccine.

**Beyond the discard point:**  
Inner square darker than outer ring.  
**DO NOT** use the vaccine.

**1**  Vaccine Cold Chain Monitor

Date in	Index	Location	Date out	Index

**2** 

**3** 

**4** **SUPPLIER**  
FOURNISSEUR

Name: \_\_\_\_\_  
Date of dispatch: \_\_\_\_\_  
Date of receipt: \_\_\_\_\_  
Vaccine: \_\_\_\_\_  
Vaccine: \_\_\_\_\_

**5** Keep the Cold Chain Monitor with your vaccine

When the Monitor arrives . . . . .  
complete the top part of the card  
- fill in the date  
- fill in the index (-, A, B, C and/or D)  
- fill in the location

When the Monitor leaves . . . . .  
complete the top part of the card  
- fill in the date  
- fill in the index (-, A, B, C and/or D)

If windows A, B, C & D are all white use vaccines normally.

If the windows A to C are completely blue, but window D is still white it means that the vaccine has been exposed to a temperature above 10°C but below 34°C for the following number of days:

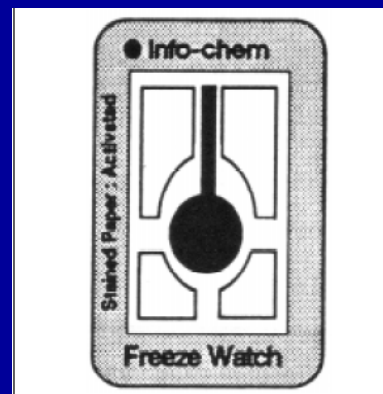
	INDEX		
	A	AB	ABC
At a temperature of 12°C	3 days	8 days	14 days
At a temperature of 21°C	2 days	6 days	11 days

If window D is blue it means that there has been a break in the cold chain of a temperature higher than 34°C for a period of at least two hours. Check the cold chain.

The instruction - use within three months should not be followed if either the expiry date or any local cold chain policy requires a shorter period before use or disposal of the vaccine.

Assembled & distributed by Berlinger Ganterschwil Switzerland

**6**



# Transporting IMP

## The Cooler Box

- Use a validated system
  - courier companies have various packaging types, each designed to maintain temperature for a specific amount of time
  - choose one for twice the time needed
  - ice packs need to be pre-frozen at the right temperature for the right time
- Remember that cold could damage your IMP as badly as heat
  - Shields between the IMP and ice-packs are essential

# CONGRATULATIONS



**Now You Know All You Need To  
Know About Temperature Storage  
Control**

