醫療器材GDP環境監控與溫度測繪實務

張仁豪 Daniel Chang
台灣大昌華嘉股份有限公司
醫療保健事業部
品質暨醫藥事務處長

Oct 15th, 2021

Delivering Growth – in Asia and Beyond.

Agenda

1 前言

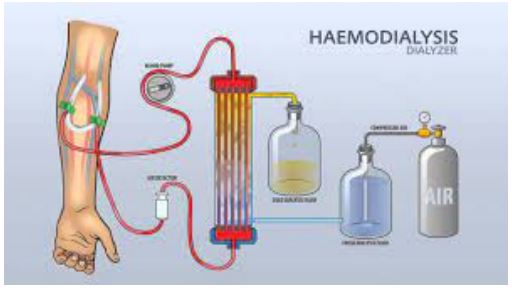
不只藥品 醫療器材品質與效能也需考量溫度

Laboratory Reagents

Ophthalmic Viscosurgical Devices OVDs

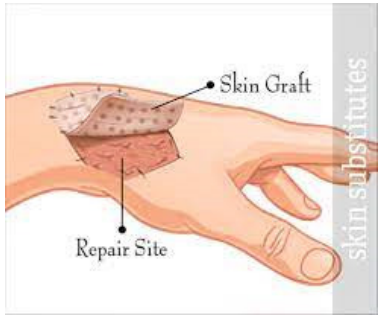
Human Heart Valve Allografts

Organ Preservation/Storage Solutions



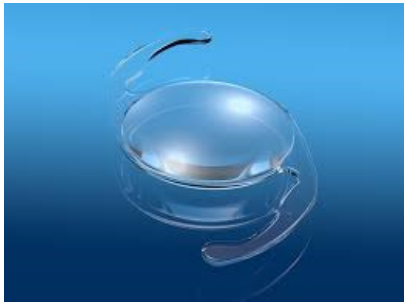
Dialyzers

Dental Products



Skin Substitutes and Burn Products

Heparin Lock Flush Syringe



Intra-Ocular Lenses (IOLs)

Ref 圖片取自網路僅用做教學使用

醫療器材供應鏈中的溫度風險
Temperature Risk in Medical Device Supply Chain

製造廠	海運 空運	物流中心	陸運 空運	醫院或零售醫材商
產品規格 包裝方式	一般貨櫃或 空調貨櫃	廠區溫控與監測	車輛溫度確效 包裝確效	零售器材商與醫院 的儲存環境 零售器材商到醫院 與客戶端的配送

是否全程考量產品特性與儲存運輸的條件?

Ref: Distribution Center PNG: https://www.pngegg.com/en/png-ytpdz/download

法源依據 - 醫療器材優良運銷準則

第 13 條

販賣業者應就運銷系統，以書面訂定基礎設施之條件，並應符合產品要求，避免產品混淆及其處理失序。

前項設施，應包括儲存、作業場所、運輸車、冷藏（凍）庫，及工作環境管制、監控與量測所用設備。

第一項設施之維護、確效及校正，應以書面訂定其內容、方式及頻率，並製作紀錄及保存；其內容包括下列事項：

一、確保用於運輸、儲存或處理醫療器材之車輛及設備符合產品之規格，且裝備適當。

二、儲存區於開始使用前進行初步之溫度測繪及風險評估，並依其評估結果放置溫度監測器。

三、對於溫度敏感之醫療器材，應使用確效後之設備進行監控；其證明或使用許可，由適當人員開立及核准。

四、建立設備非預期失序之立即處置程序，維持醫療器材品質。

第 14 條

販賣業者應就運銷系統，以書面訂定工作環境規範；其訂定應考量溫度、濕度及其他外部有害因素，並應予以監控及管制。

2 風險為基礎的環境監測

風險為基礎的環境監測
Risk-based Approach for Environmental Monitoring

產品規格

- 溫度敏感性
- 安定性考量
- 零配件
- 包裝方式

儲存與運輸

- 溫層
- 儲存區域
- 運輸方式

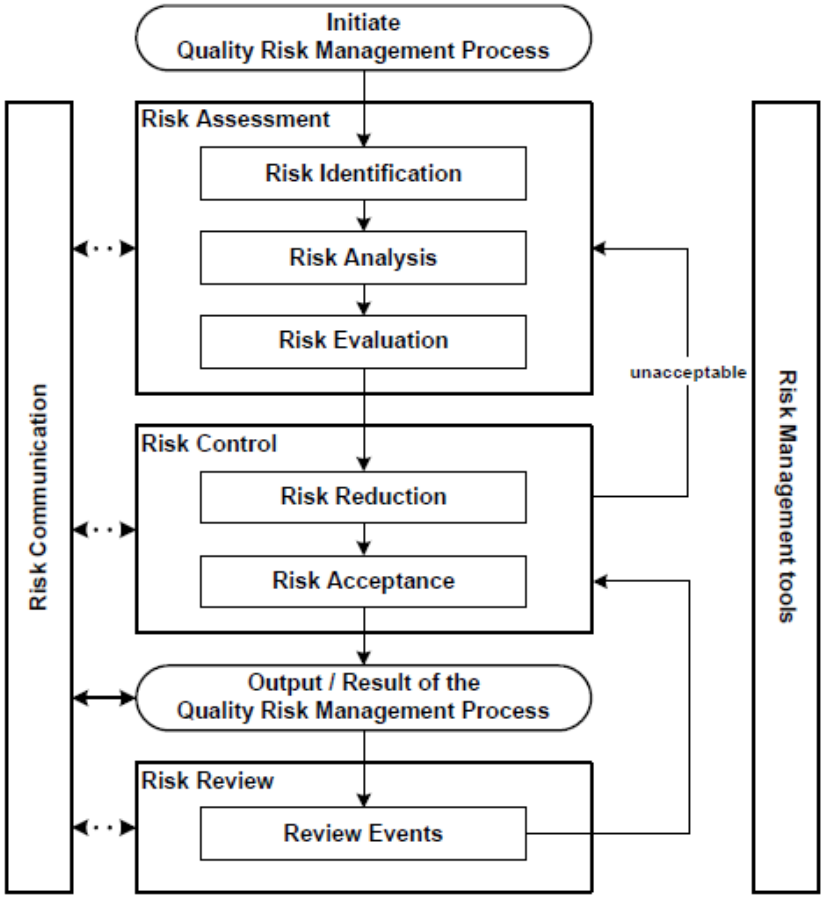
溫度測繪

- 量測設備
- 校正
- 佈點 (考量風險)

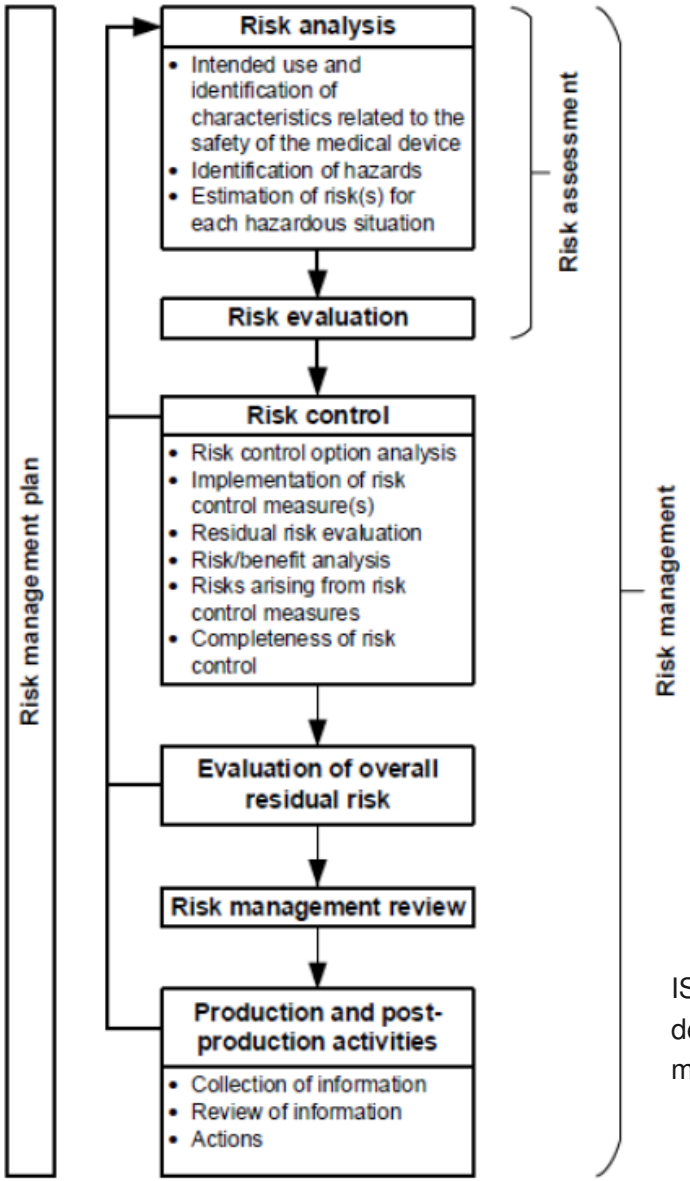
溫度監控

- 預防性保養
- 最劣點 Worst case監控與管制
- 監測方式
- 警示系統
- 緊急應變

風險管理流程



ICH Q9 Quality Risk Management (pharmaceutical quality)



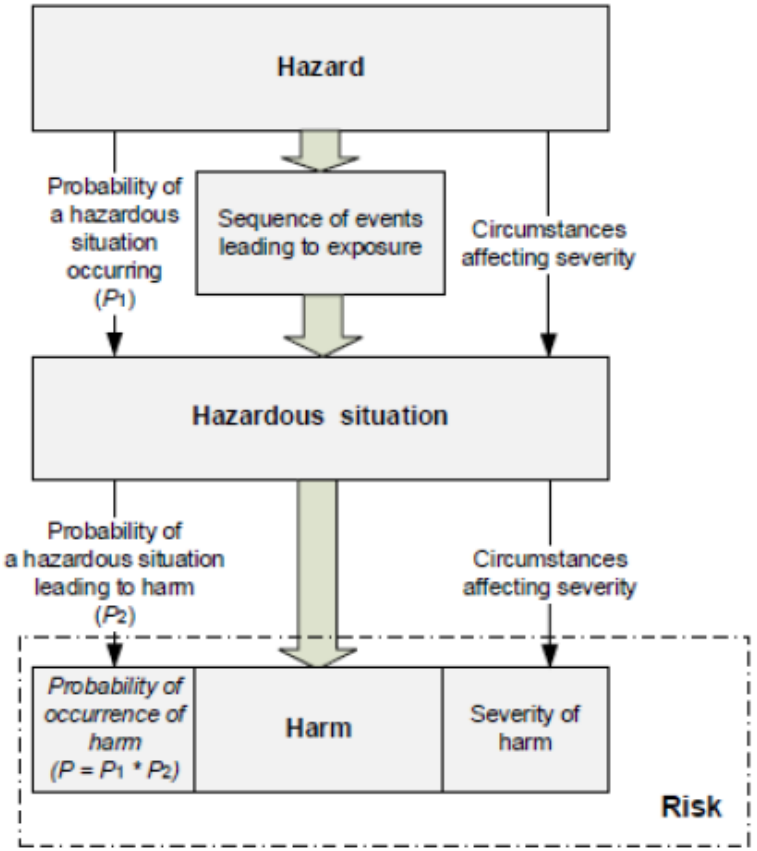
ISO 14971:2019 Medical devices — Application of risk management to medical devices

考量對產品的有害因素

舉例: 危害、可預見的事件順序、危害情境與傷害的關係

危害 Hazard	可預見的事件順序 Foreseeable sequence of events	危害情境 Hazardous situation	傷害 Harm
溫度	(1)環境溫度未控制 (2)儲存環境的溫度未經測繪 (3)高風險的區域未監控 (4)冰箱開關時間、頻率…	產品暴露於高溫或低溫環境超出產品規格 造成產品變質	(1)病患使用到不良醫療器材未達預期效能 (2)不良反應
濕度	…		
光照	…		
壓力	…		
…			

依據產品規格特性列舉



3 溫度測繪方法與實務

環境監測與溫度測繪的標準

- WHO Technical Report Series, No.961, 2011 Annex 9

  Model guidance for the storage and transport of time- and temperature–sensitive pharmaceutical products

- Technical supplement to WHO Technical Report Series, No. 961, 2011

  Supplement 8 Temperature mapping of storage areas, 2015

However, Pharmaceutical products do not include medical devices

- WHO Technical Report Series, No. 957, 2010 Annex 5

  WHO good distribution practices for pharmaceutical products :

  Although medical devices are not included in the definition of pharmaceutical products for the purposes of this document, the main principles established in this document may also be used where applicable for medical devices.

- The methodology of temperature mapping may also be referenced by Medical Devices industry

產品儲存條件 – 溫層

用詞	中譯	原文
Temperature 溫度	冷凍：低於-15 ℃ 冷藏：+2 到+8 ℃ 低溫：+8 到+ 15 ℃ 室溫：+15 到+ 25 ℃ 環境溫度：非冷藏藥品所需的儲存溫度；通常於產品上標示為「儲存於25 ℃ 以下」或「儲存於30 ℃ 以下」。	Deep freeze : Below -15 ℃ In a refrigerator : +2 to +8 ℃ Cold or Cool: +8 to + 15 ℃ Room Temperature: +15 to + 25 ℃ Ambient: The required storage temperature of non refrigerated medicinal product; usually stated on the product as ‘store below 25 ℃’ or ‘store below 30 ℃’.

Ref: PIC/S GDP, PE011-1

溫度測繪的4個階段
Four stages of the temperature-mapping process

a) Prepare a mapping protocol. 準備溫度測繪計劃書

b) Carry out the mapping exercise. 執行溫度測繪活動

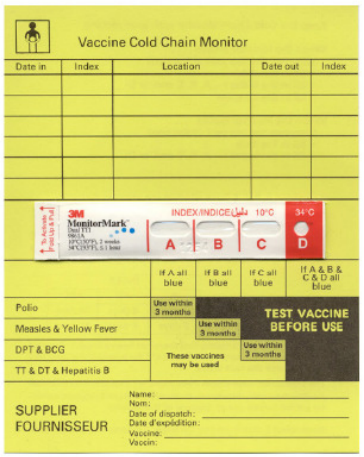
c) Prepare a mapping report. 準備測繪報告

d) Implement the recommendations by carrying out the remedial and other actions identified in the mapping report. A follow-up mapping exercise may then be needed to verify the effectiveness of the remedial actions. 執行測繪報告中建議的風險改善或其他行動。後續的測繪活動可能需要以驗證風險改善行動的有效性。

可移動溫度監測設備種類
Examples of portable temperature monitoring device types

Chemical indicators (CI)

CI: Cold chain monitor card (progressive and threshold types in one card)



CI: Temptime FREEZEmarker®

Electronic temperature indicators (ETI)

Sensitech FreezeAlert™

Berlinger Q-tag® Quad

LogTag TICT-iS0°Tag®

Electronic data logging monitors (EDLM)

Libero data logger

LogTag® TRIX-8 Temperature Recorder

Accuracy of ±0.5 °C

Ref: Technical supplement to WHO TRS No. 961, supplement 15

溫度測繪設備
Associated equipment for temperature mapping

- 足夠數量的電子式溫度記錄器 – 確保空間中的溫度分布被描繪
  a sufficient number of electronic data logging monitors (EDLMs) to ensure that the temperature distribution in the space to be mapped is adequately characterized.
- 適當的電腦設備與軟體以儲存和分析資料
  suitable computer equipment and software is needed to store and analyse the data.
- EDLM必需:
  - 規格要能符合測繪與操作環境需求
  - 提供可靠的時間-溫度連續紀錄資料
  - 有適當的溫度範圍能記錄到可預期的極端溫度 (例如 –30 ℃ 至 +60 ℃);
  - 有可程式的取樣間隔，例如1分鐘至15分鐘，以及足夠的可記錄長度
  - 能追溯到國家標準，三點校正，每個校正點誤差在± 0.5 ℃
  - 能記錄並下載時間-溫度資料到電腦系統進行適當分析，且資料儲存及分析軟體符合適用的法規要求(例如: 21 CFR part 11)

溫度測繪計劃書
Temperature Mapping Protocol

計劃書包含:

a. Approval page and change control history 核准頁與變更履歷

b. Acronyms and glossary 縮寫與術語

c. Description and rationale 敘述與理由

d. Scope 範圍

e. Objectives 目標

f. Methodology 方法

g. Mapping report template 測繪報告樣板

h. Annexes as needed, including templates for the mapping report 附錄，如需要，包含測繪報告樣板

溫度測繪方法
Methodology of Temperature Mapping

Step 1 – select EDLMs 選擇電子溫度資料紀錄器

Step 2 – designate the mapping team 選定測繪團隊

Step 3 – survey the site 調查現場

Step 4 – establish acceptance criteria 建立允收標準

Step 5 – determine EDLM locations 決定電子溫度記錄器佈點

Step 6 – record EDLM 紀錄電子溫度記錄器位置與編號

Step 7 – label and program the EDLMs 標示並設定電子溫度記錄器

Step 8 – fix EDLMs in position 固定電子溫度記錄器於佈點位置

Step 9 – conduct the mapping exercise 執行溫度測繪

Step 10 – download and consolidate the data 下載並整合資料

Ref: Technical supplement to WHO Technical Report Series, No. 961, 2011, Supplement 8 Temperature mapping of storage areas, 2015

溫度測繪方法 - 步驟說明

Step 1 – select EDLMs

- 如前面所述EDLM的要求
- 要有足夠的儲存空間
- 能追溯到國家標準的三點校正
- 每個校正點誤差不超過± 0.5 ℃
- 校正記錄有效日期需登錄在溫度測繪報告
- 需考量EDLM的電池
- 應每年校正EDLM
- 確保量測一致性，每次測繪應只使用一種類型的EDLM

溫度測繪方法 - 步驟說明

Step 2 – designate the mapping team

- 需有測繪團隊 (尤其是大型倉儲，分工很重要)
- 簽名與縮寫需要留存紀錄，以追溯文件制定人員 (若有品質系統則皆有要求)
- 確保團隊成員接受所有執行工作的適當訓練 (若有品質系統則皆有要求)

Step 3 – survey the site

- 測繪區域的長度、寬度、高度
- 儲區圖面、3D立體位置圖(儲架、空調設備位置、出風口等)
- 既有的溫度監測感測器(sensor)位置

Step 4 – establish acceptance criteria

- 視該區域所需要的溫層，訂定允收標準 e.g. + 2.0 ℃ to + 8.0 ℃ or + 15.0 ℃ to + 25.0 ℃.
- 若量測需考慮開門參數，則須在測繪計畫書中描述(頻率、持續時間)

溫度測繪方法 - 步驟說明

Step 5 – determine EDLM locations

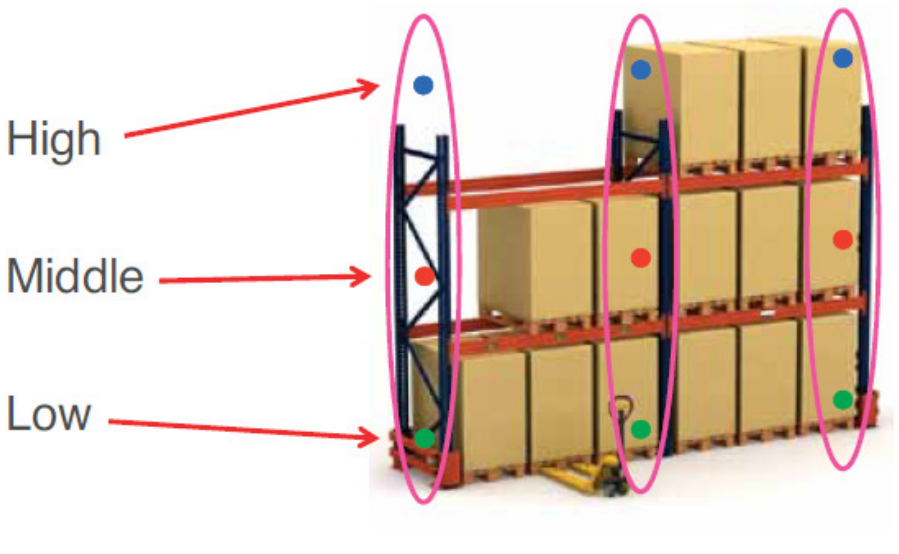
- 利用Step 4廠區調查結果佈點
- 可用風險基礎的方法來設定佈點
- 一般原則:

長度與寬度: 每 5-10M

高度:

≤ ***3.6m*** ，直接置放於每一個EDLM上方於低中高層(例如底層、1.2m、3.0m)

> 3.6m ，直接置放EDLM於底層、中間、頂部 (例如高度6M，置於0.3m、1.8m、3.6m、5.4m)



溫度測繪方法 - 步驟說明

Step 5 – determine EDLM locations

溫度佈點原則

Rule 1: 測繪極端點 Map the extremes.

Rule 2: 測繪三維空間 Map in three dimensions.

Rule 3: 大型空間，只測繪儲存區域 For large spaces, map storage only.

Rule 4: 鑑別與說明變數 Identify and address variables.

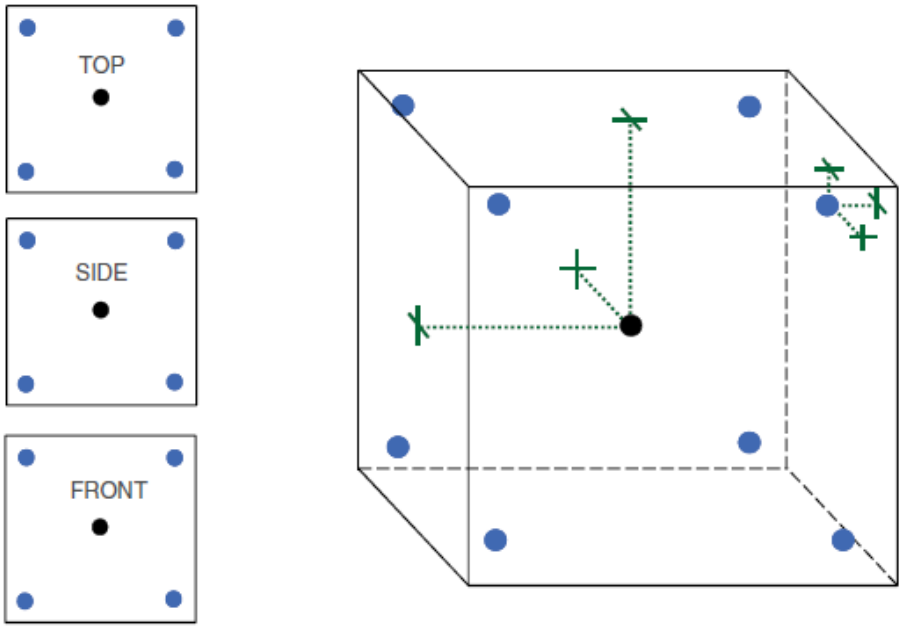
Rule 5: 如果值得測繪，就值得監測 If it's worth mapping, it's worth monitoring.

溫度測繪佈點選項

Options for temperature Mapping Points

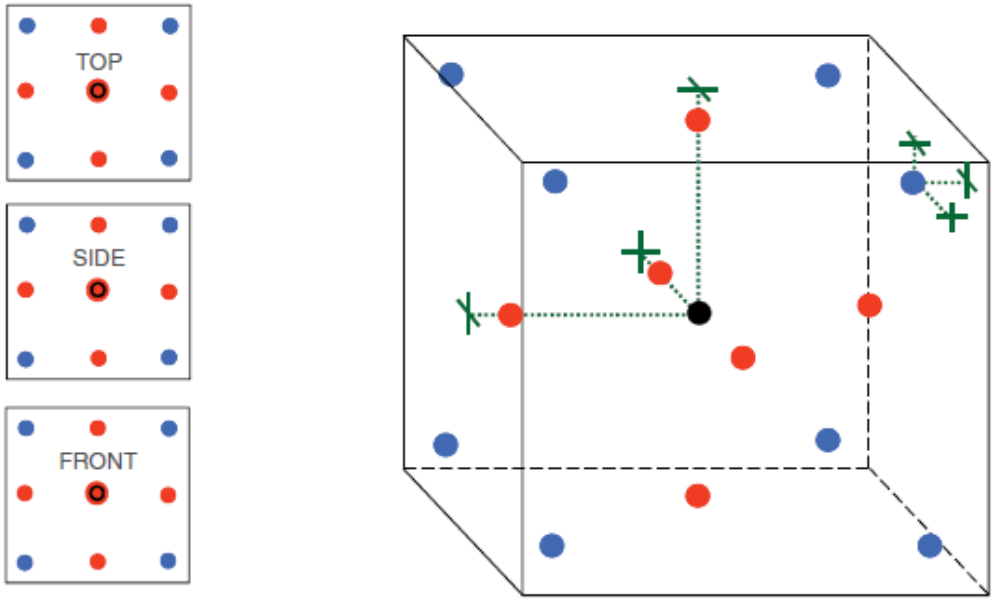
Storage Areas Up to 20m^3

A minimum of nine (9) measuring points shall be used



Storage Areas Between 21m^3 to 200m^3

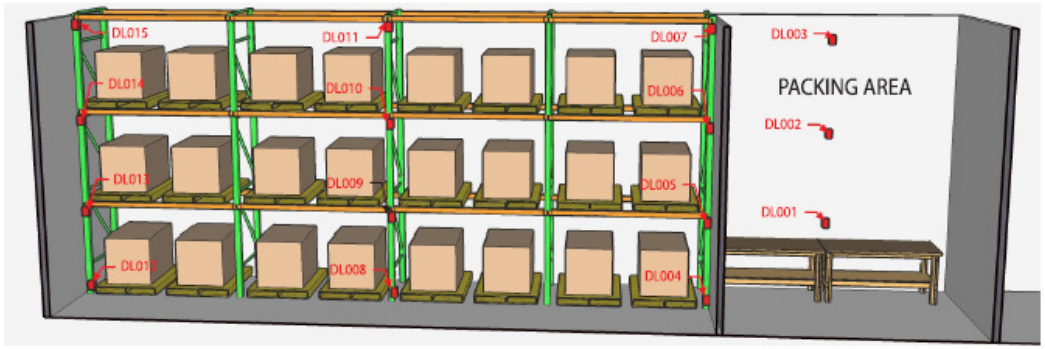
A minimum of fifteen (15) measuring points shall be used.



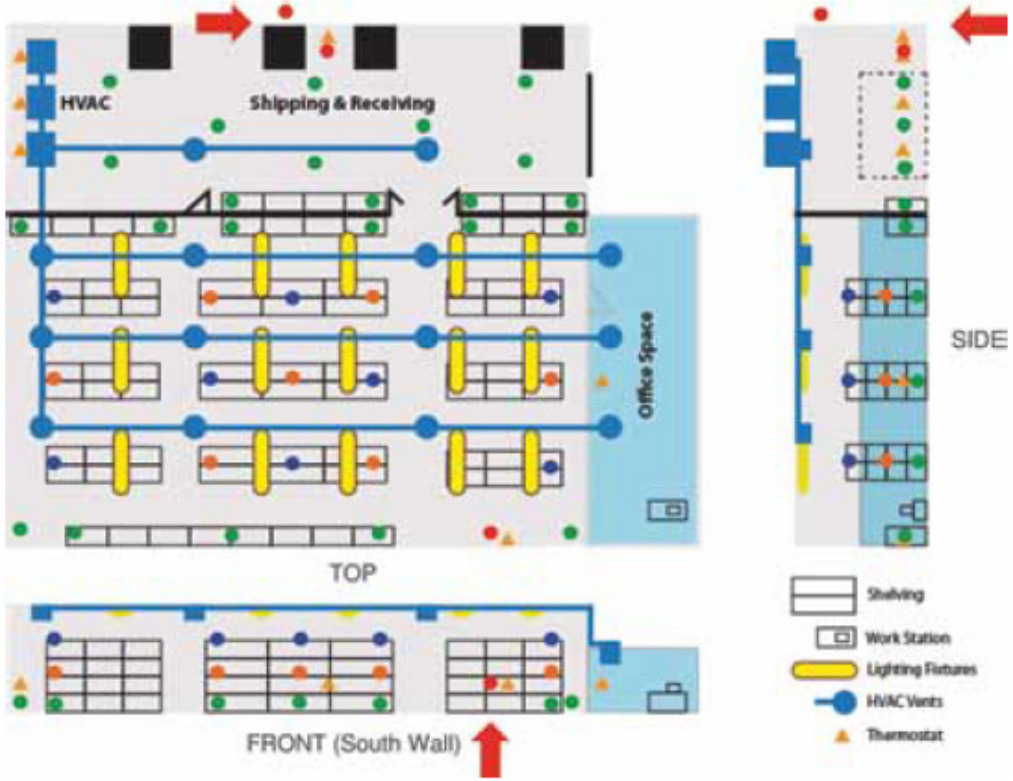
Ref: **5 Rules of Sensor Placement in Validation/Mapping Applications,** B211369EN-A, **www.vaisala.com; DKSH Regional Best Practices**

溫度測繪佈點選項
Options for temperature Mapping Points

Typical location of data loggers in a pallet racking storage area



Option 4.



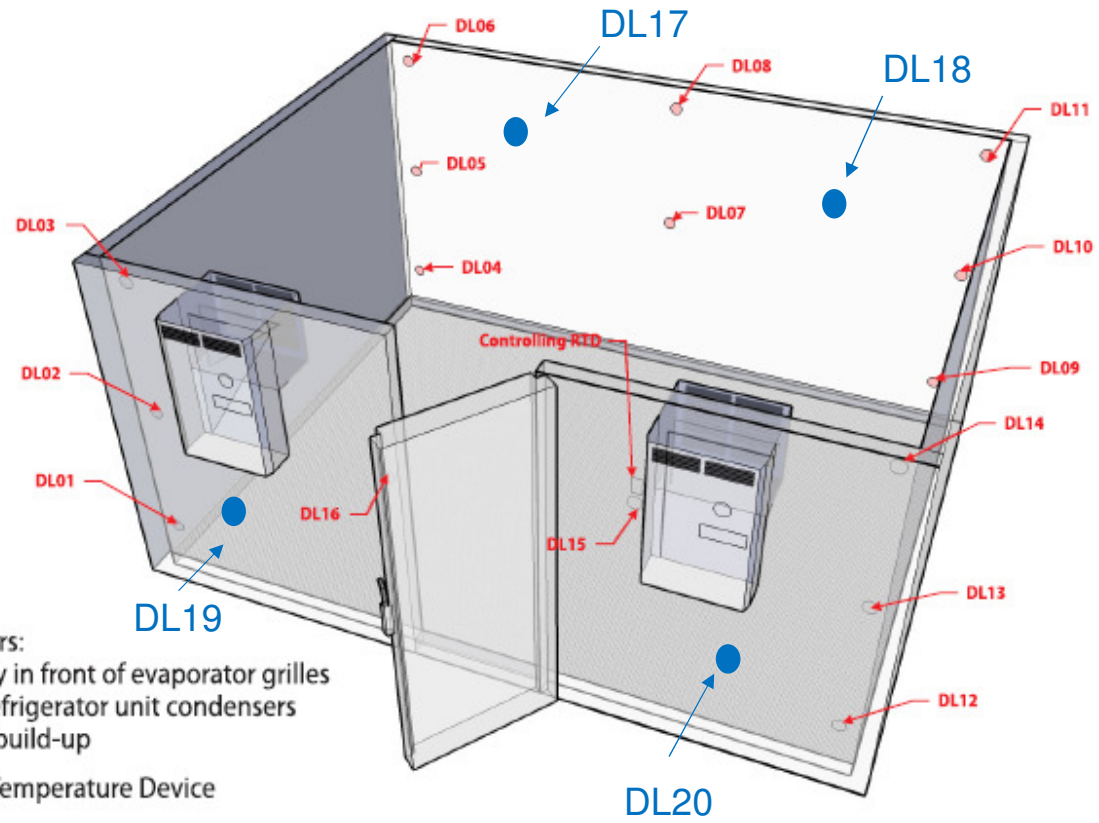
Sensor placement sample; sensors are green, blue and orange dots at different heights. Red dot of sensors to catch ambient condition

Ref: Technical supplement to WHO Technical Report Series, No. 961, 2011, Supplement 8

Ref: 5 Rules of Sensor Placement in Validation/Mapping Applications, B211369EN-A, www.vaisala.com

溫度測繪佈點選項
Options for temperature Mapping Points

Typical location of data loggers in a walk-in cold room

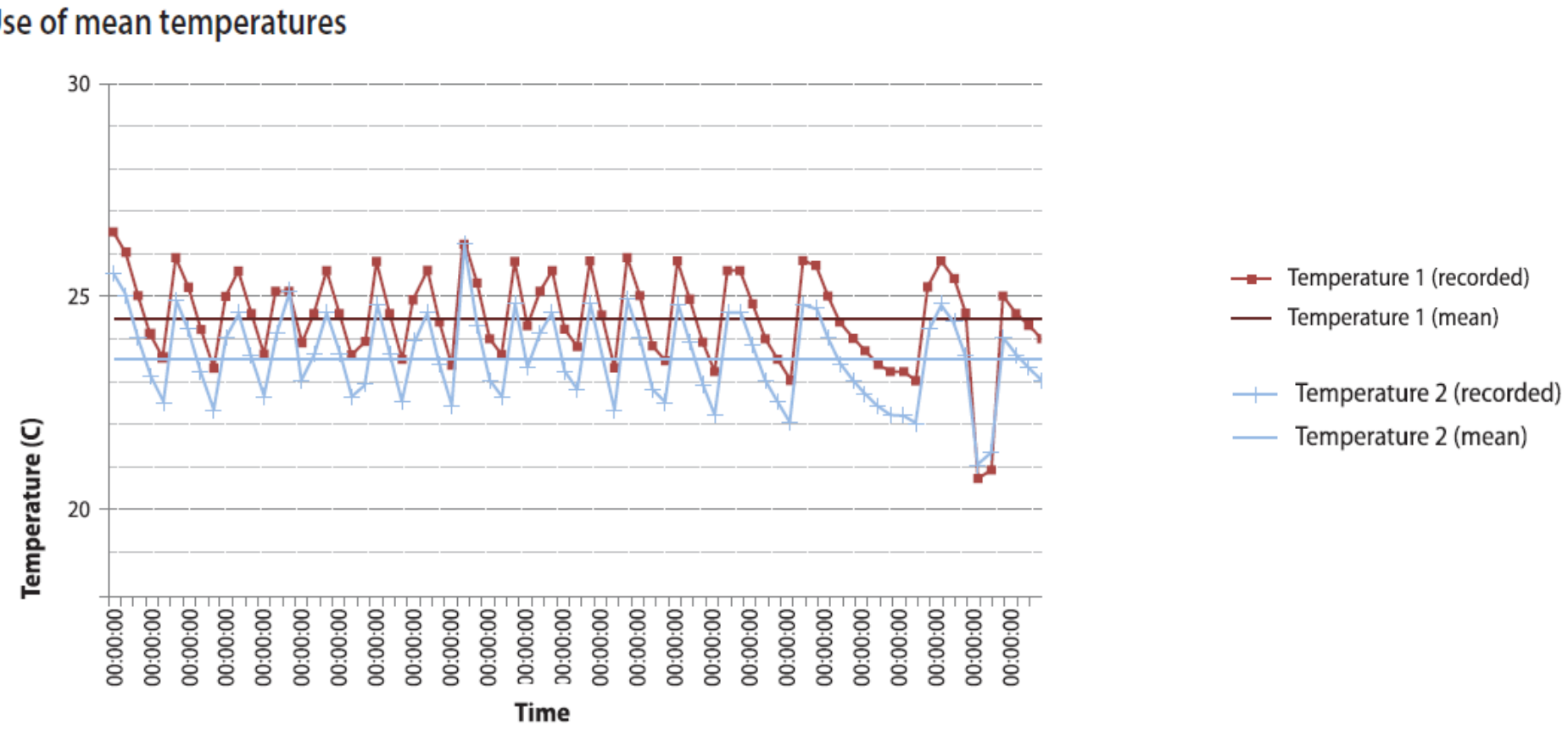


Additional sensors:
DL17, 18: Directly in front of evaporator grilles
DL19, 20: Near refrigerator unit condensers to monitor heat build-up

RTD: Recording Temperature Device

Ref: Technical supplement to WHO Technical Report Series, No. 961, 2011, Supplement 8

使用平均溫度
Use of Mean Temperatures



Ref: Technical supplement to WHO Technical Report Series, No. 961, 2011, Supplement 8

報告與紀錄範例
Example of a Template for Recording Approvals and Changes

Example of a standard template for recording approvals and changes to a document

Approvals	Name	Date	Signature
Authorized by:			
Reviewed by:			
Revised by:			
Original author:			

Version history

No.	Date	Description of change	Reason for change
1		Original	
2			
3			
4			
5			

溫度測繪資料格式範例
Example of Test Data

DKSH

Test data sheet: temperature distribution

Data logger ID number	Min. temp. recorded (°C)	Max temp. recorded (°C)	Mean temp. (°C)	Within range?		Inspected by	Date
				Yes	No		
DL-001				☐	☐		
DL-002				☐	☐		
DL-003				☐	☐		
DL-004				☐	☐		
DL-005				☐	☐		
DL-006				☐	☐		
DL-007				☐	☐		
				☐	☐		
DL-XXX				☐	☐		
Mapping period starts at (date/hour):							
Mapping period ends at (date/hour):							
Checked by:				Date:			

Door opening test sheet

Data logger ID number	Time to return to within specified temperature range (min)	Compliance?		Inspected by	Date
		Yes	No		
DL-001		☐	☐		
DL-002		☐	☐		
DL-003		☐	☐		
DL-004		☐	☐		
DL-005		☐	☐		
DL-006		☐	☐		
DL-007		☐	☐		
		☐	☐		
DL-XXX		☐	☐		
Door(s) opened at (hh:mm):					
Door(s) closed at (hh:mm):					
Checked by:		Date:			

允收標準與風險改善
Acceptance Criteria and Risk Mitigation

允收標準:

例如

- 環境溫度區不超過 30^{0}C
- 空調區不超過 25^{0}C
- 冷藏區介於2^{0}C 至 8^{0}C
- 冷凍區介於-15^{0}C 至 -25^{0}C
- 超低溫冷凍區介於-60^{0}C 至 -90^{0}C

風險改善:

例如

- 加裝機組 (需考量重新執行溫度測繪)
- 避開風險區域不要放置產品
- 控制開關門時間 (例如冷藏庫較小，或冰箱)
- 設置溫度監測器於worst case點

4 溫度監控與管制

溫度監控與管制 Temperature Monitoring and Control

- 需於最劣點(e.g. hot spot/cold spot, exit spot)設置溫度監測感測器 (Sensor)
- 考量風險因子以及季節變化，執行冬夏季或年度(或兩年一次)溫度測繪
- 設置即時警報系統(Real time alarming system)，除現場發報，並能以電話或SMS通報相關人員
- 警報系統須設定警戒值(Alarm limit, upper and lower)，並考量運作與反應時間 (response time)
- 量測儀器需定期校正
- 空調與警示系統須定期測試及預防性保養
- 關鍵設備變更及冷熱點移動須經由變更管制程序(change control process)並留存紀錄(record)

DKSH – Your Market Expansion Services Partner

We offer a broad range of tailor-made and integrated services to manage the entire value chain for our business partners.

Thank you for your attention

Delivering Growth – in Asia and Beyond.