藥品GDP倉儲及運輸溫控管理要點

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本簡報資料所使用之資訊均擷取至網路，並以教學為目的而編輯。

引言

60 Years of Discovery

Edwards

引言

GDP與風險管理

What is GDP? Purpose?

- **GDP, Good Distribution Practice, 優良運銷規範**

今日，全球化趨勢與跨國專業分工使得藥品供應鏈更加複雜，為有效確保藥品品質，藥品管理政策應涵蓋藥品供應鏈。為保障藥品從出廠後至使用前之品質，世界各國衛生主管機關對於藥品品質的要求已從過去生產面向的「藥品優良製造規範」（Good Manufacturing Practice，GMP）延伸到運銷面向的「藥品優良運銷規範」（Good Distribution Practice，GDP）。

PIC/s GMP Part I vs PIC/s GDP

章節	PIC/s GMP Part I	PIC/s GDP
一、	品質管理	品質管理
二、	組織與人事	人事
三、	廠房設施與設備	作業場所與設備
四、	文件	文件管理
五、	生產	作業
六、	品質管制	申訴、退回、疑似偽、禁藥及藥品回收
七、	委受託製造與檢驗	委外作業
八、	申訴與產品回收	自我查核
九、	自我查核	運輸

這些是否曾經發生過?

- 家裡的冰箱故障壞掉
- 颱風停電
- 冰箱的門沒關好
- 生的魚忘記放進冷凍室
- 錯拿便當

溫控產品管理的風險也和這些情節類似 !!!

(102年藥品GDP主題論壇(二)

冷藏疫苗之新聞

攪拌車拉斷電纜 冷藏疫苗險報廢

2013年06月03日 15:57:18 來源： 新華網江蘇頻道

5月23日，靖江市生祠鎮獸醫站接戶線被一輛水泥攪拌車刮斷，導致獸醫站冰櫃內冷藏的近3萬元防疫疫苗險遭報廢。

當日10時31分，靖江市生祠供電所接到生祠鎮獸醫站報修電話，稱由生祠鎮4號公用變壓器支接的400伏接戶線電纜被某中學基建施工現場一輛水泥攪拌車刮斷，導致獸醫站停電。而如果停電時間超過1個小時，儲存在獸醫站冰櫃內的近3萬元防疫疫苗將有報廢危險。

接報後，該所迅速組織人員趕往事故現場勘查。根據現場情況，該所迅速制訂搶修方案，在獸醫站準備好搶修材料後，于11時許實施搶修。該所5名搶修人員拆除斷裂電纜，架設新電纜50余米。25分鐘後，獸醫站恢復正常供電。經協商，肇事司機所在單位共賠償獸醫站搶修電纜費用1萬余元。獸醫站站長邵宏明感激地說：“真險！要不是你們迅速搶修，這批疫苗就保不住了，太感謝你們了！”（汪紅清 李 雲）

(102年藥品GDP主題論壇(二)

冷藏疫苗之新聞

5萬疫苗報廢 台中緊急調度求償

【簡體版】 【字號】大 中 小

【大紀元2011年07月06日訊】（大紀元記者黃玉燕台灣台中報導）台中市衛生局驚傳地下冷藏室的感控器在日前出現異常，導致5萬多瓶10多種3歲幼兒常規疫苗全數報廢，已經緊急由衛生署疾管局調撥。衛生局局長黃美娜6日召開說明會表示，這些疫苗佔台中市疫苗數量的1/3，主要作為調度使用，其餘已經移往各區衛生所保存，目前沒有缺貨的問題，民眾到衛生所施打的疫苗也都是安全的。

台中市衛生所傳出疫苗冷藏櫃在6月25日下午發生異常，溫度曾降到零下5度，遠低於正常保存溫度2到8度範圍內，導致價值1700萬元，5萬瓶疫苗損失慘重，其中包括B肝、日本腦炎、三合一疫苗、A肝等10多種疫苗，都是一般幼兒定期施打的疫苗。

黃美娜指出，冷藏櫃已有10年歷史，都有定期維護。她說，冷藏櫃出現異常後，27分鐘後，保全才通知衛生局，直指保全延誤通報，將請律師打求償官司。對於冷藏櫃維修廠商，也將進一步求償，若協調無果，同樣會訴諸司法。

疾管科長邱惠慈說明，因為最低溫曾下降到零下5度，疫苗可能都失效，已緊急請疾管局調撥，並強調5萬劑疫苗不會使用，民眾在各衛生所施打的疫苗，都是安全的。

冷藏疫苗之新聞

【本報訊】本港發生大規模打錯疫苗的嚴重醫療事故！衞生署昨日公布，**持牌批發商**因職員疏忽，將一批葛蘭素史克藥廠生產、三款預防流感、肺炎球菌及兒童混合劑，共二百六十支懷疑**冷凍出錯影響品質的問題疫苗，錯誤再外送**到本地私家診所、私家醫院及兩間健康院，**其中一百一十六劑更被接種**，署方未收到市民接種後不良反應的報告。有藥劑師批評事故十分嚴重，促請署方調查。

資料來源：東方日報 2011-Mar-05

人員安全的風險 – 缺氧

藥廠冷凍庫反鎖　男員工疑被活活凍死

2012年 04月 16日　16:50

社會中心／台北報導

新北市五股區1間製藥工廠今(16)日下午傳出死亡意外，1名男性員工進入冷凍倉庫後，疑似不小心被反鎖，慘遭活活凍死。目前警方已經介入調查，釐清到底是意外還是有人刻意反鎖。

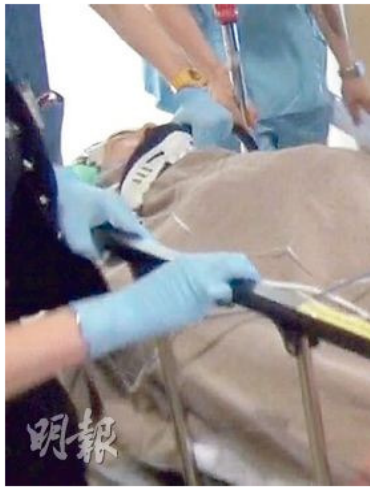
根據調查指出，藥廠設置冷凍倉庫目的是為了冰存藥品，不料卻發生意外。警方初步懷疑男子遭冷凍倉庫凍死，但也有可能是倉庫內部一氧化碳濃度較高，引發中毒身亡。

(102年藥品GDP主題論壇(二)

人員安全的風險 – 機械故障

冷藏庫電閘夾頭 工人命危

04 - 28 05:00



新入職的姓蔡工人昨與同事到大家樂食品工場維修冷藏

大家樂食品工場維修新丁出事

【明報專訊】連鎖快餐店「大家樂」位於
部的嚴重意外。一名新入職工友與另一工
取工具，折返時卻發現新入職同事被冷藏
警。救護員到場將昏迷不醒的傷者送院搶

意外令人關注是否涉及機件故障，抑或是
製造商懷疑事件涉及安全措施較遜色的舊式冷藏庫電動門，因新款冷藏庫電動門多裝有紅外線感應等安全裝備，出現嚴重夾人意外機會較微，勞工處指正調查事件（見另稿）。

行政總裁醫院探傷者

大家樂發言人證實傷者是新入職不久的僱員，公司已成立專責小組調查事故原因。大家樂行政總裁羅開光昨亦到醫院探望傷者。

報明

工友離開取物 獨留事主工作

被冷藏庫閘門夾至昏迷的工人蔡×榮（49歲），其頭、頸受傷，由救護員以擔架抬上救護車，送往沙田威爾斯親王醫院急救後，送入深切治療部留醫，截至昨晚情況危殆。事主多名親友聞訊趕至醫院了解，憂心忡忡，有女親友更激動痛哭。

涉事冷藏庫屬於大家樂的食品製作工場，工場位於大埔工業村大富街3號。昨晨9時許，蔡與一名同事到冷藏庫做例行維修保養，其間同事發現遺漏了工具，故離開取回，剩下蔡獨自工作。約10分鐘後，同事取回工具折返，發現冷藏庫閘門夾住蔡的頭，當時蔡已告昏迷，同事遂大驚報警。

救護員趕至為蔡急救，並送院治理，多名警員其後到場調查事發經過及原因。據悉，涉事的冷藏庫電動閘門約2米高，1米闊。有資深冷藏庫製造業人士指出，電動閘門多數由旁邊的開關掣啟動，亦有遙控裝置，方便運輸工人駕鏟車進出。

台灣同類意外 女工夾斃

冷藏庫電動門已不止一次「逞兇」，去年10月，台灣花蓮市亦曾發生類似意外，一名魚類加工廠的女工不慎被冷藏庫的電動閘門夾住頭部，下顎脫臼，頸椎斷裂，送院後傷重不治。

(102年藥品GDP主題論壇(二)

風險 = 嚴重度 x 發生機率

運銷階段	可能發生的問題	造成的結果	嚴重程度	發生的機率
國際運輸	.....	.....		
大型倉儲	送錯貨	注射變質藥品 (無效/嚴重副作用)		
	機械故障	人員傷亡		
	.....			
當地運輸	.....			
醫療院所	電線拉斷(停電)	藥品失溫 (高溫失效)		
	機件故障	藥品失溫 (低溫失效)		
	.....			

(102年藥品GDP主題論壇(二)

為何需要“溫控管理”？

因為風險高，所以溫控產品更需要嚴密地管理

(102年藥品GDP主題論壇(二)

溫控產品物流

範例模擬 國外製造廠運送藥品到台灣物流倉儲再運銷到醫院

	Origin Port	International Transport	Destination Port	Warehouse/ Distributor	Domestic Transport	Hospital/Pharmacy
作業	• 倉儲 • 出貨	• 空運 • 海運	• 海關 • 陸運	• 收貨 • 倉儲 • 出貨	• 陸運 • 空運 • 海運	• 收貨 • 倉儲 • 調劑
設備	主動式：Cold Container , Envirotainer … 被動式：整棧板保冷包裝			Cold Room (walk-in-refrigerator)	Cold Box or Vehicle	Refrigerator
挑戰	貨運時間比預期久，外在環境溫度惡劣(停機坪、港口…不能遮風避雨, 無溫控)			停電、機件故障、包裝錯誤、貨量驟增減	道路航班狀況、外在環境溫度、客戶拒收	驗收程序、冰箱條件與設備、發藥與使用、調貨轉院
管理	委外包商管理、確效、物料管理			確效、預防保養、預警、備援、技能訓練	委外包商管理、確效、物料管理	確效、預防保養、預警、備援、技能訓練、運輸管理

從啟運到使用者收到藥品的這段期間，都要**確保溫控**產品的**溫度維持在標示的倉儲溫度。**

(102年藥品GDP主題論壇(二)

風險 = 嚴重度 x 發生機率

運銷階段	可能發生的問題	造成的結果	嚴重程度	發生機率	預防方式
國際運輸	**運輸時間超出保溫包裝極限**	藥品失溫(高溫失效)			使用主動式冷藏包裝
大型**倉儲**	送錯貨	注射變質藥品 (無效/嚴重副作用)			區隔不同狀態產品 (待驗、放行、報廢) 之儲區
	停電	藥品失溫 (高溫失效)			使用**備用發電機**
	機件故障	人員傷亡			設置緊急求救裝置和安全警示裝置
		藥品失溫 (高溫/低溫失效)			**預防保養**包括重要零件的備品
	存貨量暴增/減	藥品失溫 (高溫/低溫)			**冷藏室確效**
	……				
當地**運輸**	道路中斷、天氣太冷、車溫太高	藥品失溫 (高溫/低溫)			**保溫箱確效** **車溫監控**
醫療院所	電線拉斷(停電)	藥品失溫 (高溫失效)			使用備用發電機
	機件故障	藥品失溫 (低溫失效)			**準備備援計畫**
	……				

(102年藥品GDP主題論壇(二)

引言

GDP基礎概念

PIC/s GDP 基本範圍

Warehousing

Transportation

Distance ⟺ Capability of Controlling Temperature

Storage → Picking → Packing → Delivery → Customer

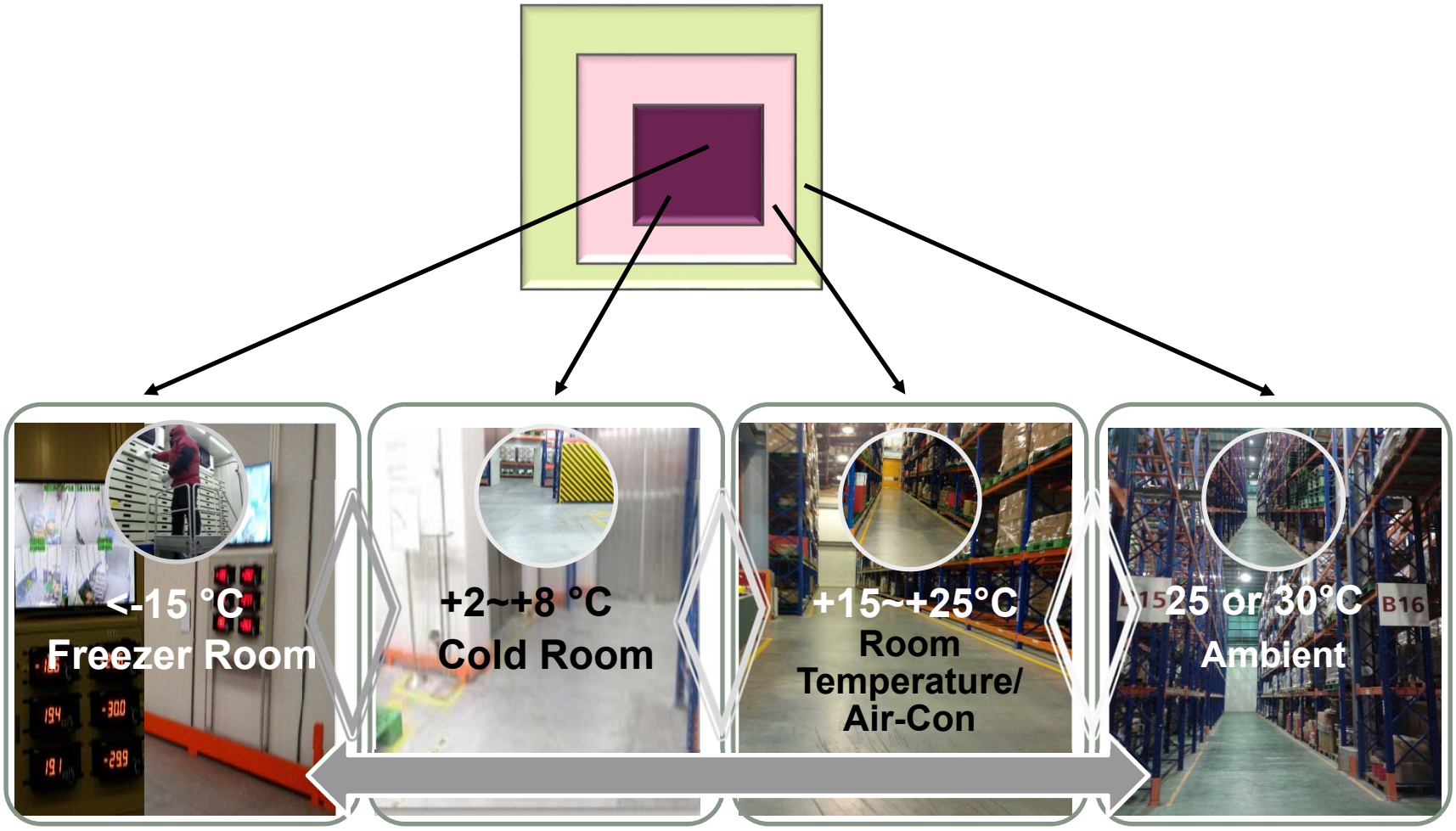
Definition of Storage Temperature
儲存溫度之定義

用詞	中譯	原文
Temperature 溫度	冷凍: 低於-15°C 冷藏: +2到+8°C 低溫: +8到+15°C 室溫: +15到+25°C 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°C以下」或「儲存於30°C以下」	Deep freeze: Below -15°C In a refrigerator: +2 to +8°C Cold or Cool: +8 to +15oC Room Temperature: +15 to +25°C Ambient: The required storage temperature of non refrigerated medicinal product; usually stated on the product as "store below 25°C" or "store below 30°C".

(Feat. PIC/s GDP, PE011-1)

Basic Design of Different Temperature Storage Area

不同溫層儲存區之基本設計



To prevent influences on product quality from door opened between different temperature storage area.

藥品GDP倉儲溫控管理要點

藥品GDP倉儲溫控管理要點

倉儲作業溫控要點相關GDP法規及參考文件

Reference for GDP Guideline on Storage Temperature
儲存溫度之GDP法規及參考文件參照表

Item	Chapter	Description	Reference
第 3 章	作業場所及設備		
3.1	原則		
		批發運銷商必須具備適當且足夠的作業場所、配備及設備，以確保能夠適當儲存及運銷藥品，此作業場所必須是潔淨、乾燥及**維持在可接受的溫度範圍**內。	WHO TRS No. 961, Annex 9 Sec. 4, Temperature-controlled storage Sec. 6, Transport and delivery
3.3	溫度及環境管制		
	3.3.1	**應具備適當的設備及程序以確認藥品的儲存環境**。需考量的環境因素包括作業場所的**溫度**、濕度、光線及清潔。	WHO TRS No. 961, Annex 9 Sec. 4, Temperature-controlled storage
	3.3.2	**儲存區應在代表性的條件下於開始使用前進行初步的溫度測繪評估**。溫度監測設備應依照測繪評估結果設置，以確保監測設備是位於歷經極端溫度波動的位置。溫度測繪評估應依風險評估於有重大改變時重複執行。若為數平方公尺之小型常溫作業場所，應執行潛在之風險評估(如冷或暖氣機)，並依照其評估結果放置溫度監測器。	WHO TRS No. 961, Annex 9 Sec. 4, Temperature-controlled storage Technical supplement to WHO TRS No. 961, Annex 9

(Feat. PIC/s GDP, PE011-1)

Reference for GDP Guideline on Storage Temperature
儲存溫度之GDP法規及參考文件參照表

Item	Chapter	Description	Reference
第 3 章	作業場所及設備		
3.4	設備		
	3.4.1	影響儲存及運銷藥品之所有設備應依照符合其預定目的的標準設計、設置、維護及清潔。**操作具重要功能的關鍵設備，應規劃進行維護保養**。	WHO TRS No. 961, Annex 9 Sec. 4, Temperature-controlled storage Technical supplement to WHO TRS No. 961, Annex 9/ Supplement 12 Technical supplement to WHO TRS No. 961, Annex 9/ Supplement 15
	3.4.2	**用於管制或監測藥品儲存環境之設備**，應依風險與可靠性評估結果，在界定的**時間間隔進行校正**。	WHO TRS No. 961, Annex 9 Sec. 4, Temperature-controlled storage
	3.4.3	**設備的校正應可被追溯到國家或國際量測標準**。設備應具備適當的警報系統以在**偏離預定儲存條件時發出警報**，且設定適當地警報級別，並定期測試警報以確保功能正常運作。	WHO TRS No. 961, Annex 9 Sec. 4, Temperature-controlled storage
	3.4.5	**應製作關鍵設備的維修、維護及校正作業紀錄**，並保存結果。關鍵設備如冰庫、監測入侵者警報與入口管制系統、冷藏庫、溫濕度計或其他溫度與濕度記錄裝置、空氣處理裝置及供應鏈內使用的任何設備。	WHO TRS No. 961, Annex 9 Sec. 4, Temperature-controlled storage

(Feat. PIC/s GDP, PE011-1)

Reference for GDP Guideline on Storage Temperature
儲存溫度之GDP法規及參考文件參照表

Item	Chapter	Description	Reference
第 3 章	作業場所及設備		
3.6	驗證及確效		
	3.6.2	**設備與流程在開始使用前及任何重大變更後(如維修或維護)應分別驗證或確效**。	WHO TRS No. 961, Annex 9 Sec. 4, Temperature-controlled storage Technical supplement to WHO TRS No. 961, Annex 9
	3.6.3	應準備確效與驗證報告，總結說明獲得的結果及評論任何觀測到的偏差；偏差應文件化並採取進一步行動以矯正偏差及避免重複發生，必要時應適用矯正預防措施(CAPA)。**合格確效的證明及流程或設備的許可應由適當的人員製作及核准**。	WHO TRS No. 961, Annex 9 Sec. 4, Temperature-controlled storage Technical supplement to WHO TRS No. 961, Annex 9

(Feat. PIC/s GDP, PE011-1)

Reference for GDP Guideline on Storage Temperature
儲存溫度之GDP法規及參考文件參照表

Item	Chapter	Description	Reference
5.5	儲存		
	5.5.1	**藥品與保健食品(必要時)應與其他可能改變藥品(或保健食品)本質的**產品分開儲存，且不得受到光線、溫度、濕度及其他外部有害因素的影響；**需要特定儲存條件之**產品應特別注意。	WHO TRS No. 961, Annex 9 Sec. 4, Temperature-controlled storage
	5.5.2	必要時，進廠藥品之容器在儲存前應予以清潔。對進廠貨物進行的任何行為（如煙燻），不得影響到藥品品質。	WHO TRS No. 961, Annex 9 Sec. 4, Temperature-controlled storage
	5.5.3	**倉儲作業須確保維持適當的儲存條件且提供適當的庫存安全**。	WHO TRS No. 961, Annex 9 Sec. 4, Temperature-controlled storage

(Feat. PIC/s GDP, PE011-1)

藥品GDP倉儲溫控管理要點

倉儲作業溫控要點基礎要求

Temperature Control and Monitoring in Storage
儲存溫度控制及監視

1. **Temperature control 溫度控制**
   - System able continuously to maintain air temperatures within the set point limits through the validated storage volume
   - Control sensors accurate to **+/- 0.5 °C or better**
   - Control sensors shall be calibrated
   - Control sensors positioned at the **"hot" and "cold" spots** determined by temperature mapping, even if affected by door opening
   - Control sensors independent of the temperature monitoring system
2. **Temperature monitoring 溫度監視**
   - Monitoring sensors accurate to **+/- 0.5 °C or better for electronic devices** and **+/- 1 °C or better for alcohol, bi-metal gas or vapor pressure thermometers**
   - Monitoring sensors shall be calibrated
   - Monitoring sensors positioned so as to be minimally affected by transient events such as door opening
   - Temperature monitoring devices, temperature traces or electronic temperature records manually checked **"at least twice a day"**, **in the morning and evening, seven days a week, including public holidays**

(Feat. WHO TRS No. 961, Annex 9)

Humidity Control and Monitoring in Storage
儲存濕度控制及監視

1. **Humidity control 濕度控制**
   - Provide humidity control in temperature-controlled rooms that are used to store **time and temperature-sensitive pharmaceutical products, TTSPPs** which aversely affected by high relative humidity and are not sufficiently protected by their packaging. Such products are typically labelled “store in a dry place”, or carry similar wording and require a humidity-controlled environment.
2. **Humidity monitoring 濕度監視**
   - Sensors accurate to **+/- 5 % RH**
   - Sensors shall be calibrated
   - Sensors located to monitor **worst-case humidity levels** within the qualified storage volume
   - **Sensors positioned so as to be minimally affected by transient events such as door opening**
   - Provides a humidity record with a minimum recording frequency of **“six times per hour”** for each sensor position

(Feat. WHO TRS No. 961, Annex 9)

Alarm systems 警示系統

1. **Temperature alarms 溫度警示**
   - Sensors accurate to **+/- 0.5 ºC or better**
   - Sensors shall be calibrated
   - Sensors located to monitor **worst-case** temperature within the validated storage volume, sensors should be located close to the temperature monitoring sensors
   - **Sensors positioned so as to be minimally affected by transient events such as door opening**
   - High/low alarms set points to trigger appropriately located **visual alarms**, **audible alarms** for temperature-controlled rooms, cold rooms and freezer rooms
   - Preferably there should be an **automatic telephone dial-up or SMS text warning system** to alert on-call personnel when an alarm is triggered outside working hours for temperature-controlled rooms, cold rooms and freezer rooms

(Feat. WHO TRS No. 961, Annex 9)

Alarm systems 警示系統

2. Humidity alarms

- Sensors accurate to **+/- 5 % RH**
- Sensors shall be calibrated
- Sensors located to monitor **worst-case** humidity level within the validated storage volume, sensors should be located close to the humidity monitoring sensors
- **Sensors positioned so as to be minimally affected by transient events such as door opening**
- High/low alarms set points to trigger appropriately located **visual alarms**, **audible alarms**
- Preferably there should be an **automatic telephone dial-up or SMS text warning system** to alert on-call personnel when an alarm is triggered outside working

(Feat. WHO TRS No. 961, Annex 9)

Calibration and Verification of Control and Monitoring Devices 控制及監視儀器之校正及驗證

1. **Calibration of temperature control and monitoring devices**
   - Calibrate devices against a certified, traceable reference standard **"at least once a year"**
   - Calibration should demonstrate the accuracy of the unit **"across the entire temperature range"** over
   - Single-use devices that are supplied with a manufacturer's calibration certificate do not need to be re-calibrated
2. **Calibration of humidity control and monitoring devices**
   - Calibrate devices against a certified, traceable reference standard **"at least once a year"**
   - Single-use devices that are supplied with a manufacturer's calibration certificate do not need to be re-calibrated
3. **Alarm equipment verification**
   - Check functionality of temperature and humidity alarms **"at least once every six months"** at the designated set points
   - Maintain records to demonstrate compliance

(Feat. WHO TRS No. 961, Annex 9)

藥品GDP倉儲溫控管理要點

倉儲區溫度描繪作業

Four Stages for Temperature Mapping Exercise
溫度描繪作業之四階段

1. **Prepare mapping protocol**

2. **Carry out the mapping exercise**

3. **Prepare a mapping report**

4. **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.**

(Feat. Technical supplement to WHO TRS No. 961, Annex 9)

Prepare Mapping Protocol 準備溫度描繪計畫書

a. Approval page and change control history

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			

(Feat. Technical supplement to WHO TRS No. 961, Annex 9)

Prepare Mapping Protocol 準備溫度描繪計畫書

b. Acronyms and glossary

c. Description and rationale

d. Scope

- **Two times for each area/per study**
- **Consider the effect of seasonal variation**
- **Subsequent mapping exercises must also be carried out on a periodic basis – for example, every three years – in order to demonstrate continuing compliance.**

e. Objectives

- Mapping temperature variations within the selected storage areas
- Measuring temperature variations at each location within the chosen area
- Documenting high and low temperature
- Identifying potential airflow issue that may affect temperature
- Identifying the best places to locate temperature sensors

(Feat. Technical supplement to WHO TRS No. 961, Annex 9)

Prepare Mapping Protocol 準備溫度描繪計畫書

f. Methodology

1. Select **EDLMs**(**E**lectronic **D**ata **L**ogger **M**onitor), which should have a **NIST-traceable 3-point** calibration and the error **no more than +/- 0.5 ºC**
2. Designate the mapping team
3. Survey the site
4. Establish acceptance criteria
5. Determine EDLM locations,

For length and width: every 5-10 M

For height: ceiling height is

< 3.6 M, high and low level, e.g. in height of 3.6 M, put floor, 1.2 M and 3.0 M

> 3.6 M, bottom, middle and top, e.g. in height of 6.0 M, put 1.8 M, 3.6 M and 5.4 M

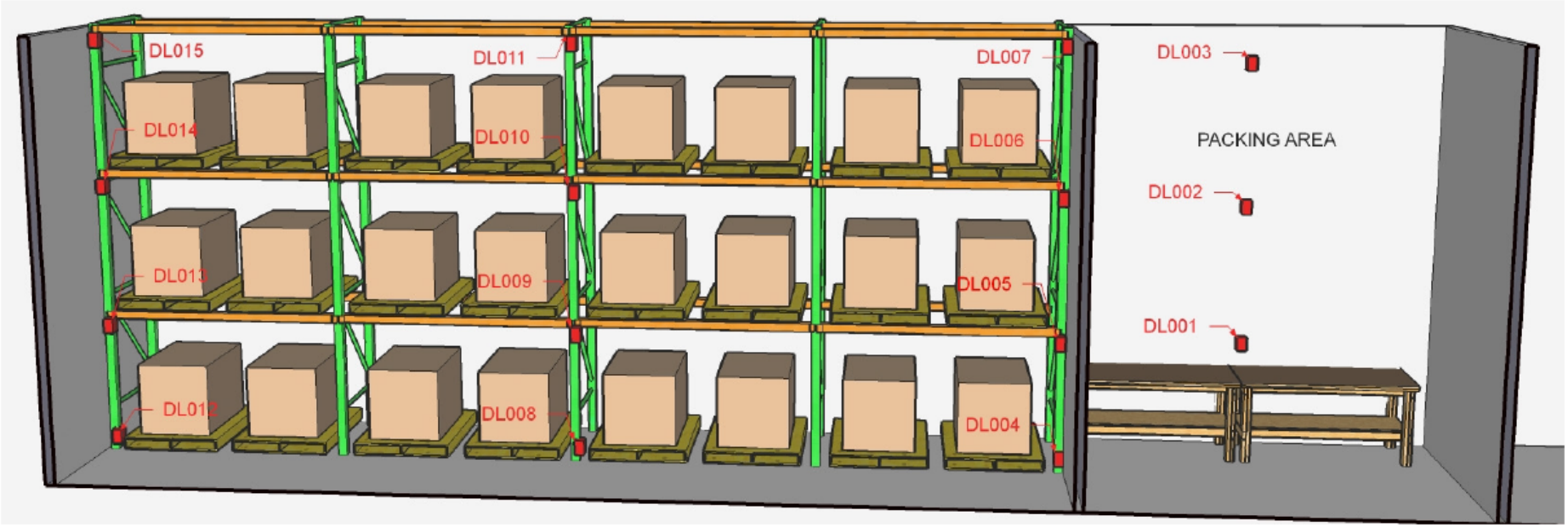
(Feat. Technical supplement to WHO TRS No. 961, Annex 9)

Prepare Mapping Protocol 準備溫度描繪計畫書

- **Methodology**

5. Determine EDLM locations

Figure 1 – Typical location of data loggers in a pallet racking storage area



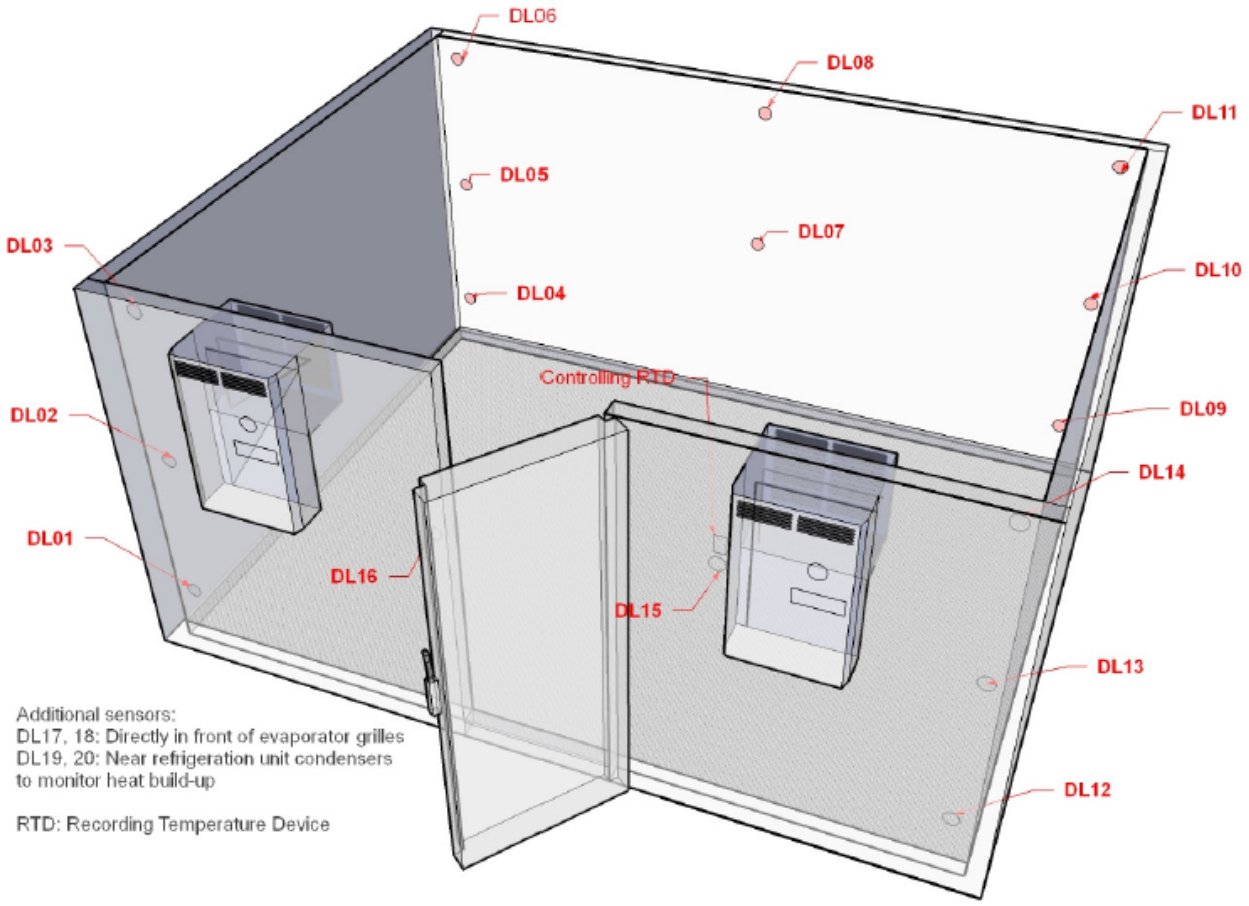
(Feat. Technical supplement to WHO TRS No. 961, Annex 9)

Prepare Mapping Protocol 準備溫度描繪計畫書

- **Methodology**

5. Determine EDLM locations

Figure 2 – Typical location of data loggers in a walk-in cold room



(Feat. Technical supplement to WHO TRS No. 961, Annex 9)

Prepare Mapping Protocol 準備溫度描繪計畫書

- **Methodology**

6. Record EDLM and thermostat locations
7. Label and program the EDLMs, typically recorded would be set between 5 and 15 minutes

A1.1 Test data sheet: temperature data logger locations

Data logger ID number	Data logger serial number	ID number on schema	Mounting ht (metres)	Description / Comments
DL-001		1	0.3	
DL-002		2	2.8	
DL-003		3	5.4	
DL-004		4	0.3	
DL-005		5	2.8	
DL-006		6	5.4	
DL-007		7	0.3	
DL-008		8	2.8	
DL-009		9	5.4	

(Feat. Technical supplement to WHO TRS No. 961, Annex 9)

Prepare Mapping Protocol 準備溫度描繪計畫書

- **Methodology**

7. Label and program the EDLMs, typically recorded would be set between 5 and 15 minutes

A1.2 Test data sheet: temperature distribution

Thermostat Information		
Location	Set point	Comment
Near entrance door #1	20C	Locked
Near loading dock #4	20C	Locked

(Feat. Technical supplement to WHO TRS No. 961, Annex 9)

Prepare Mapping Protocol 準備溫度描繪計畫書

- **Methodology**
  8. Fix EDLMs in position
  9. Conduct the mapping exercise

  – **Seven to 10 consecutive days for “warehouse and other ambient storage areas”**

  – **24 to 72 hours for “temperature-controlled equipment”**

(Feat. Technical supplement to WHO TRS No. 961, Annex 9)

Prepare Mapping Protocol 準備溫度描繪計畫書

- **Methodology**

10. Download and consolidate the data

A1.3 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	18.6	22.4	20.5	☒	☐	JB	
DL-002				☐	☐		
DL-003				☐	☐		
DL-004				☐	☐		
DL-005				☐	☐		
DL-006				☐	☐		
DL-007				☐	☐		
DL-008				☐	☐		
DL-009				☐	☐		

(Feat. Technical supplement to WHO TRS No. 961, Annex 9)

Prepare Mapping Protocol 準備溫度描繪計畫書

g. Mapping report template

a) Introduction

b) Summary

c) Conclusions and recommendations

d) Report annexes

h. Annexes as needed, including templates for the mapping report

(Feat. Technical supplement to WHO TRS No. 961, Annex 9)

Various Temperature Device types 溫度記錄器種類

Chemical indicators (CI), chemical time-temperature integrators (CTTI)

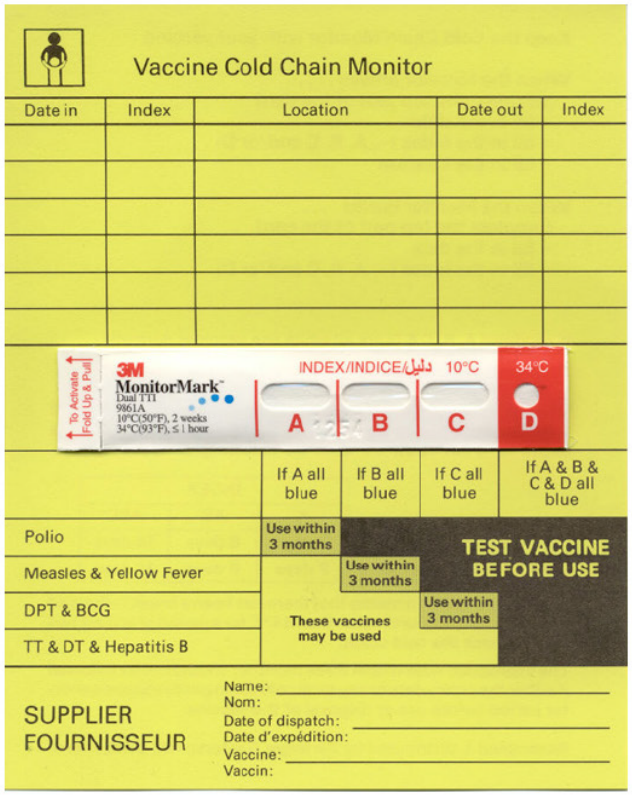
CI: TempTime LIMITmarker™ device – threshold indicator for high temperature

CI: Temptime FREEZEmarker®

(Feat. Technical supplement to WHO TRS No. 961, supplement 15)

Various Temperature Device types 溫度記錄器種類

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



CTTI: Vaccine vial monitor

(Feat. Technical supplement to WHO TRS No. 961, supplement 15)

Various Temperature Device types 溫度記錄器種類

Electronic temperature indicators (ETI)

Sensitech FreezeAlert™

Berlinger Q-tag® Quad

LogTag TICT-iS0°Tag®

(Feat. Technical supplement to WHO TRS No. 961, supplement 15)

Various Temperature Device types 溫度記錄器種類

Electronic data logging monitors (EDLM)

Libero data logger

LogTag® TRIX-8 Temperature Recorder

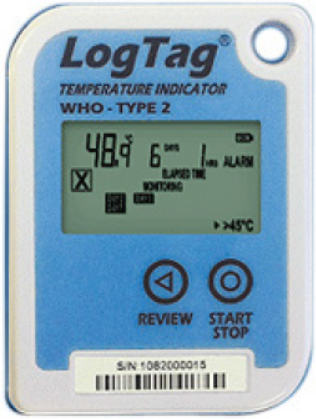
(Feat. Technical supplement to WHO TRS No. 961, supplement 15)

Various Temperature Device types 溫度記錄器種類

Electronic data integrators (EDI)

Berlinger Q-tag® CLm Doc

LogTag® TIC20



VaxAlert™ Temperature Indicator

(Feat. Technical supplement to WHO TRS No. 961, supplement 15)

Various Temperature Device types 溫度記錄器種類

Electronic temperature monitoring and event logger systems (TMEL)

Transcan Sentinel with thermal printer

(Feat. Technical supplement to WHO TRS No. 961, supplement 15)

Storage - Distribution and Warehouse

- 規格：依照儲存貨品溫度需求以及貨品數量設計合適的溫控庫房
- 安全： Walk in refrigerator (Cold Room、冷鏈庫房) 為低溫之密閉空間，為了作業人員之安全著想，應考慮提供員工保暖衣物，以及裝置人身安全相關之設備(例如：氧氣偵測器、緊急求救設備、監視錄影等)
- 溫度監測：應有溫度測繪、安裝溫度計於冷/熱點、溫度偏差的警報裝置
- 緊急應變：應有緊急應變措施以處理停電、設備故障等問題並定期演練 (包括逃生路線、緊急停止機械運作)

(102年藥品GDP主題論壇(二)

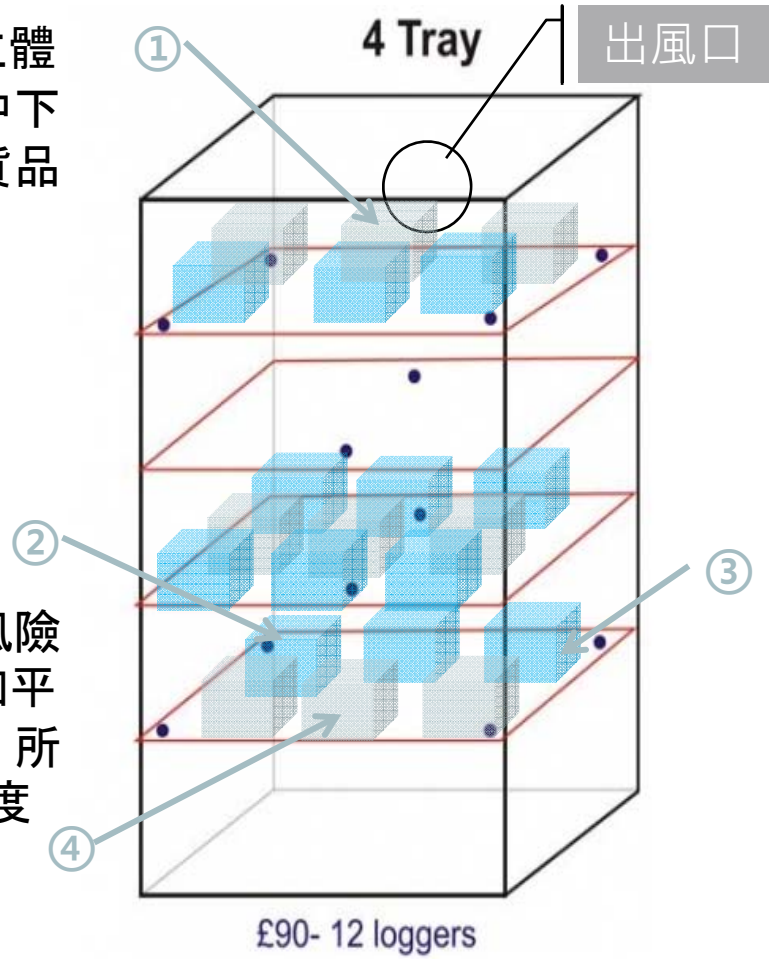
Temperature Mapping of Storage Area
儲存區之溫度描繪

1. 先準備好要測繪的圖
   - 要有尺寸 (才能決定平均鋪陳要放幾點)
   - 要有設備的相關位置 (才能決定高風險位置的點)
     - 高風險位置：門邊、風口、風扇背面、死角....
   - 每個位置要編註號碼才能勾稽溫度資料
2. 準備足量的溫度計(必須是連續式的溫度記錄器)，溫度計的設定都要調整成一致 (例如每幾分鐘記錄一次)
3. 確定空調設備的各項參數(要記錄下來)
4. 紀錄倉儲區的使用率 (滿載和空載)：**新建倉儲需執行空滿載，但如果是已經啟用的倉儲僅需執行滿載**
5. 決定測試期間每天開關門幾次(模擬正常的作業狀況)
6. 決定可以接受的合格標準 (例如溫度幾度)
7. 寫成 Protocol

(102年藥品GDP主題論壇(二)

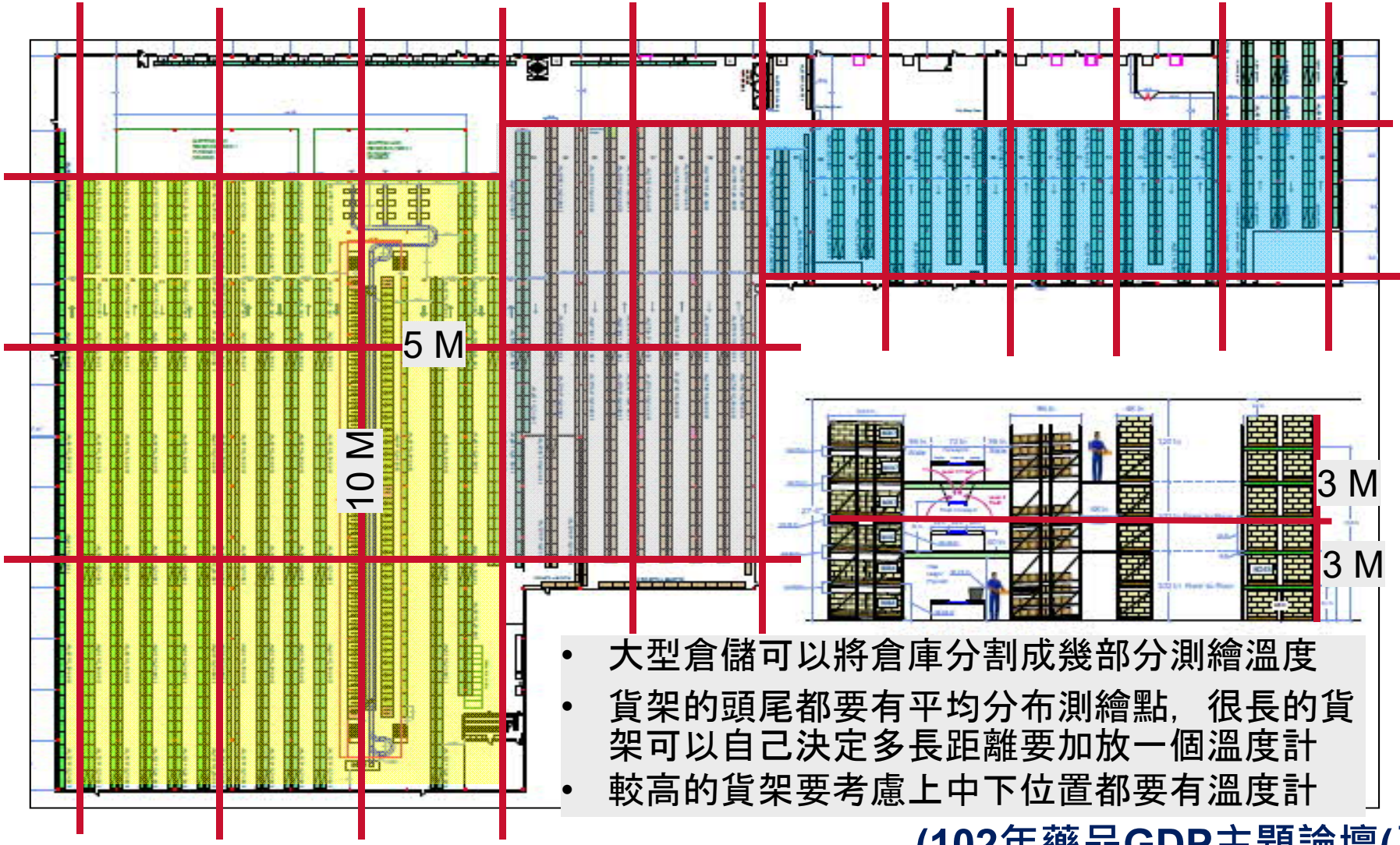
Location of Temperature-Monitoring Devices for Mapping of Storage Area (i.e. Refrigerator)

- 平均分布的位置 - 用立體空間的想法，注意上中下前後左右，只要會放貨品的位置都要兼顧
- 高風險位置
  - 冷風直吹 ①
  - 吹不到冷風 ② ③
  - 溫度忽高忽低 ④
- 以右圖為例，四處高風險位置有兩處 (② ③)和平均鋪陳的測繪點重疊，所以共有14 位置要掛溫度計 (4-2+12=14)



(102年藥品GDP主題論壇(二)

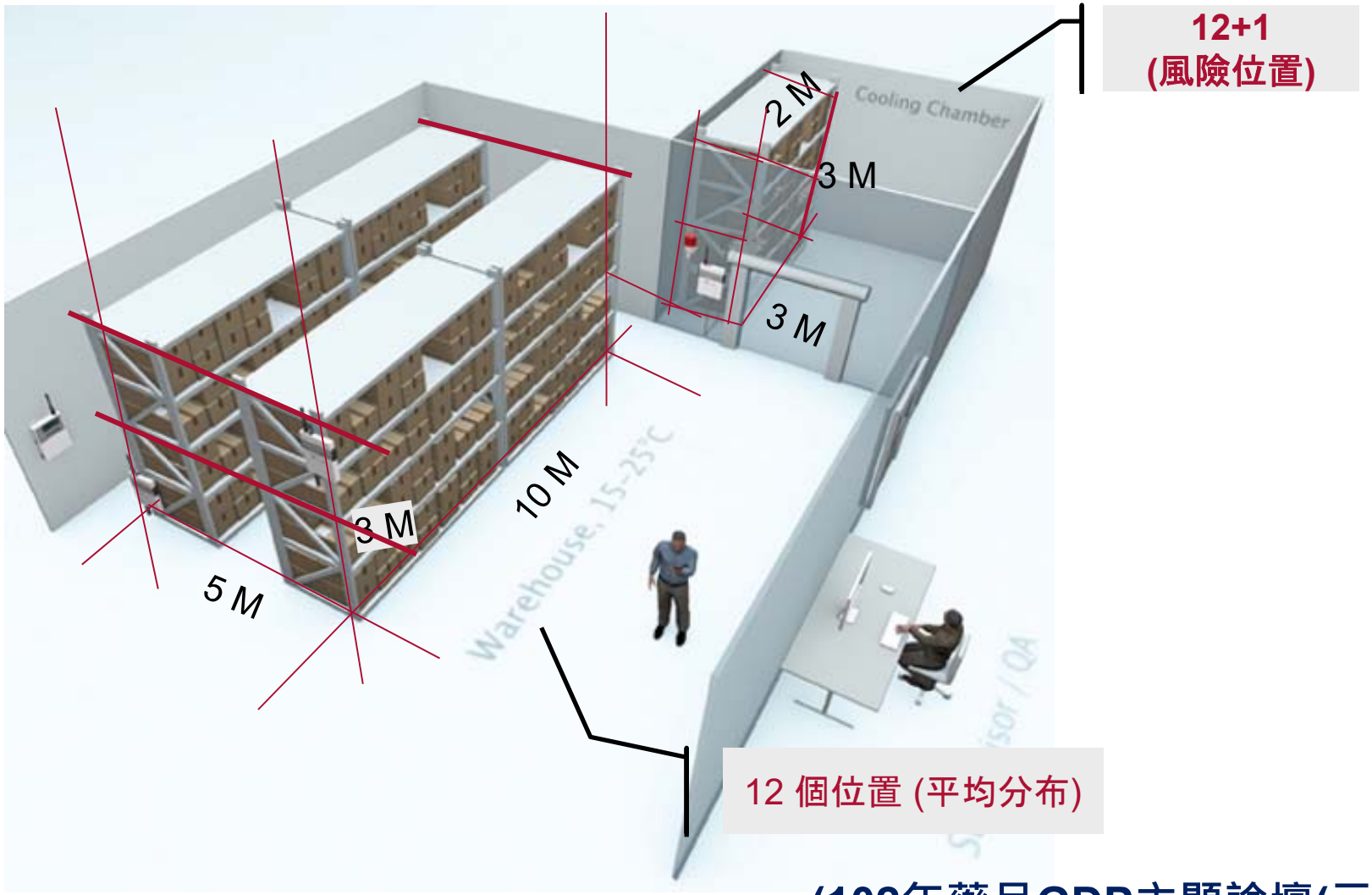
Template of Location for Pallet Racking Storage Areas
貨架儲存區溫度記錄器放置位置範本



- 大型倉儲可以將倉庫分割成幾部分測繪溫度
- 貨架的頭尾都要有平均分布測繪點，很長的貨架可以自己決定多長距離要加放一個溫度計
- 較高的貨架要考慮上中下位置都要有溫度計

(102年藥品GDP主題論壇(二)

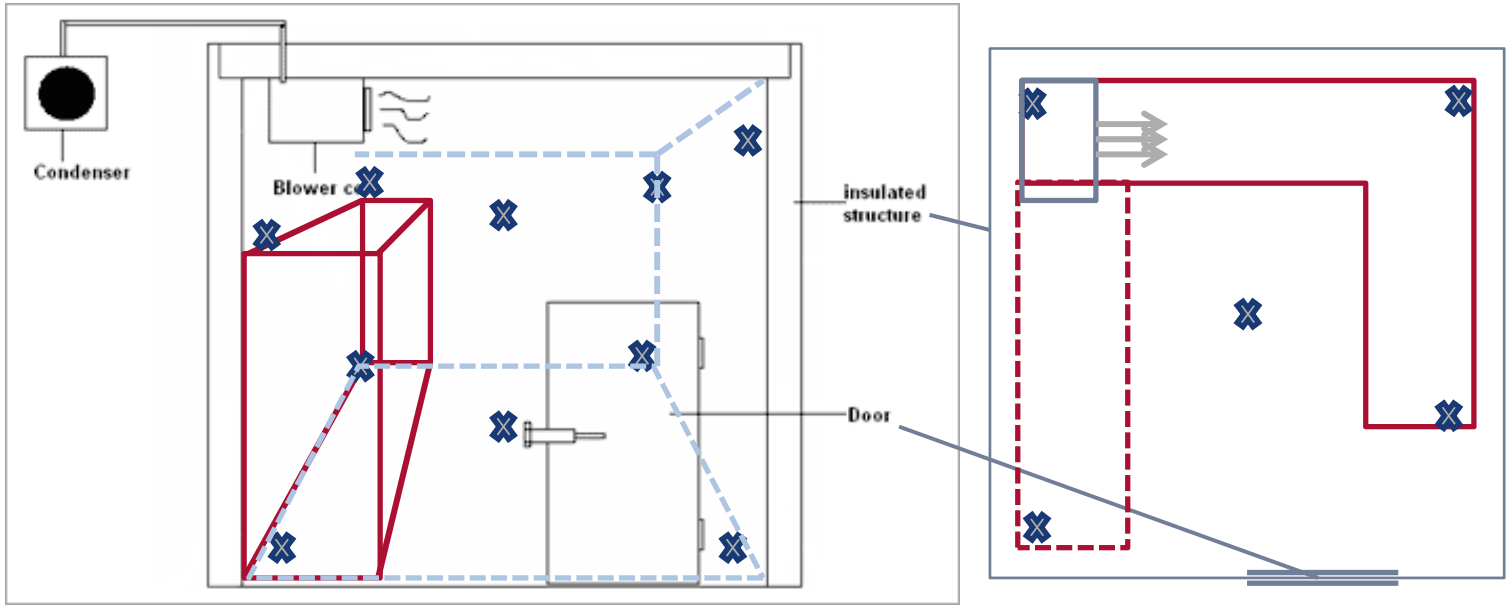
Template of Location for Walk-in Temp-Controlled Room
溫控區溫度記錄器放置位置範本



(102年藥品GDP主題論壇(二)

Key Points if Temperature Mapping
溫度描繪之要點

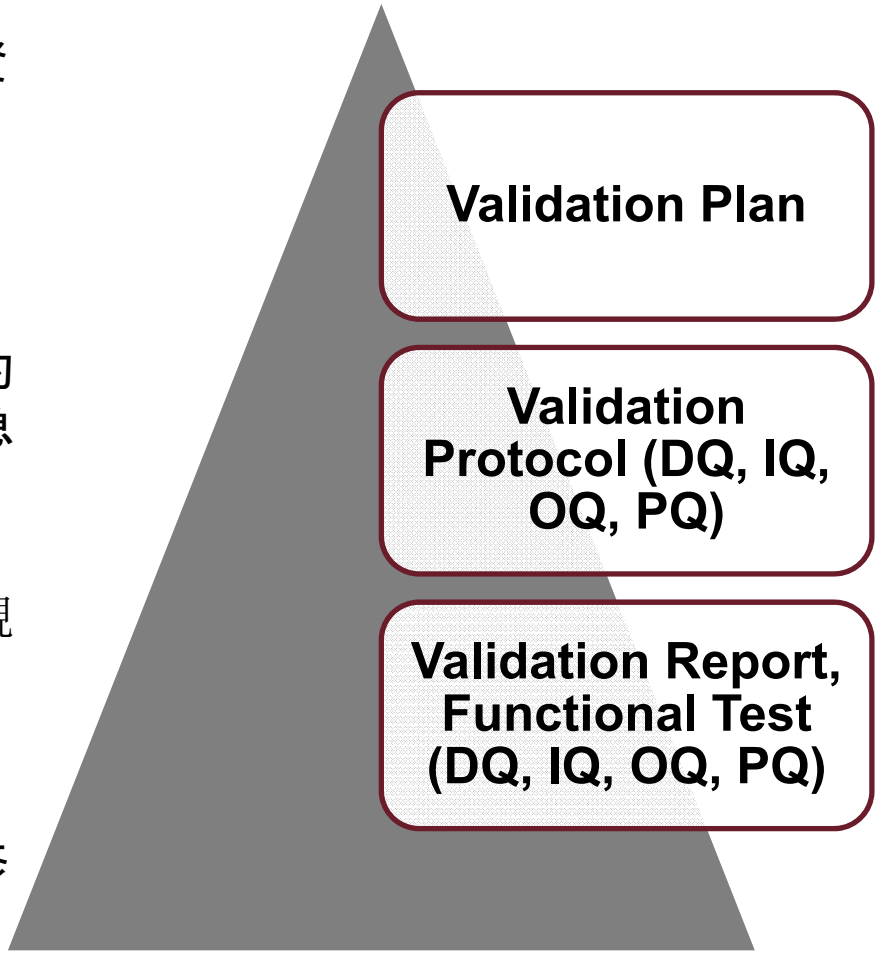
- 儲存區應在代表性的條件下於開始使用前，進行初步的溫度測繪試驗。
- 溫度監測設備應依照測繪試驗結果設置，以確保監測設備是位於歷經極端溫度波動的位置 (最冷點與最熱點)。
- 溫度測繪試驗應依風險評估或當設施或溫度監測設備有重大改變時重複執行。
- 溫度測繪的點，應將"貨品實際放置位置" 考慮進去



(102年藥品GDP主題論壇(二)

Key Points of Validation of Temperature-Controlled Areas
溫控區確效要點

- DQ – 當初設計溫控區的各項相關資料
- IQ –溫控區的硬體設備資料、教育訓練資料(無教育訓練就無法操作)、操作手冊SOP、校正報告與安裝時之基本測試.....等等
- OQ –溫控區的降溫能力是否能夠依照設定值變化、溫控區的保溫能力、溫控區的各項警報是否會依照設計要求發報、緊急設備是否會依照原設計啟動功能....等等
- PQ – 溫度測繪證明溫控區設備持續運作一段時間後依然可以維持室內溫度符合規定、開關門測試(確定正常情況作業下溫度不會產生偏差)，溫度測繪時要注意空載與滿載的差異....
- RQ – 再驗證，一段時間或重大變更/維修後，應再次驗證其性能



(102年藥品GDP主題論壇(二)

Temperature Monitoring – Storage Areas
儲存區之溫度監視

- 依照溫度測繪的結果在 “冷/熱點” 位置掛上溫度計，監督最差位置的溫度
- 應有人員每天檢查與紀錄溫控區的溫度
- 除了檢查溫度之外，也應巡視各機件的功能是否正常，特別是備用發電機、警報器等緊急狀況的特別設備，更應定期測試

藥品GDP運輸溫控管理要點

藥品GDP倉儲溫控管理要點

運輸作業溫控要點相關GDP法規及參考文件

Reference for GDP Guideline on Transport Temperature
運輸溫度之GDP法規及參考文件參照表

Item	Chapter	Description	Reference
第 9 章	運輸		
9.1	原則		
	9.1.1	批發運銷商的職責，是在供應藥品時防止藥品破損、摻假、竊盜，及**確保在運送時維持在可接受的溫度條件下**。	WHO TRS No. 961, Annex 9 Sec. 6, Transport and delivery
	9.1.2	在任何運送模式下，都應能夠證明藥品不會暴露在可能危害藥品品質及完整性的狀況，且應基於風險考量規劃運輸路線。	WHO TRS No. 961, Annex 9 Sec. 6, Transport and delivery Technical supplement to WHO TRS No. 961, Annex 9/ Supplement 12 Technical supplement to WHO TRS No. 961, Annex 9/ Supplement 15
	9.2.5	溫度管制需求應依運送路線的風險評估決定。運送時，在車輛及裝存箱櫃內用於監測溫度的設備，應定期進行維護及校正。	WHO TRS No. 961, Annex 9 Sec. 6, Transport and delivery
	9.2.6	運送藥品時，應盡可能使用專用的車輛與設備；使用非專用的車輛與設備時，應有適當的程序以確保不會危及藥品品質及完整性。	WHO TRS No. 961, Annex 9 Sec. 6, Transport and delivery

(Feat. PIC/s GDP, PE011-1)

Reference for GDP Guideline on Transport Temperature
運輸溫度之GDP法規及參考文件參照表

Item	Chapter	Description	Reference
第 9 章	運輸		
9.3	裝存箱櫃、包裝及標示		
	9.3.1	藥品應在對**品質不會產生不良作用及適當保護其免受外在影響(如污染)之裝存箱櫃**中運送。	WHO TRS No. 961, Annex 9 Sec. 6, Transport and delivery Technical supplement to WHO TRS No. 961, Annex 9/ Supplement 12
	9.3.2	選擇裝存箱櫃及包裝時，應考量藥品儲存與運送的要求、藥品數量所需的空間、預期外部極端溫度、儲存在海關過境之最長時間、**包裝的驗證狀態**及**運輸容器的確效狀態**。	WHO TRS No. 961, Annex 9 Sec. 6, Transport and delivery Technical supplement to WHO TRS No. 961, Annex 9/ Supplement 12

(Feat. PIC/s GDP, PE011-1)

Reference for GDP Guideline on Transport Temperature
運輸溫度之GDP法規及參考文件參照表

Item	Chapter	Description	Reference
第 9 章	運輸		
9.4	需要管制條件的產品		
	9.4.3	**對於溫度敏感的產品，應使用經驗證的設備(例如保溫包裝、溫控裝存箱櫃或溫控車)**，以確保產品在製造商、批發運銷商及客戶間運送時，維持在正確的運輸條件。	WHO TRS No. 961, Annex 9 Sec. 6, Transport and delivery Technical supplement to WHO TRS No. 961, Annex 9/ Supplement 12 Technical supplement to WHO TRS No. 961, Annex 9/ Supplement 15
	9.4.4	溫控車在運送時所使用的溫度監測設備應定期進行維護及校正，並於**代表性條件下執行溫度測繪，且應考量季節變化(必要時)**	WHO TRS No. 961, Annex 9 Sec. 6, Transport and delivery Technical supplement to WHO TRS No. 961, Annex 9 Technical supplement to WHO TRS No. 961, Annex 9/ Supplement 12
	9.4.6	**在隔熱箱使用保冷劑時，須放在不會與產品直接接觸之處**，員工必須接受組裝隔熱箱(季節性配置)及重複使用保冷劑相關程序之訓練。	WHO TRS No. 961, Annex 9 Sec. 6, Transport and delivery Technical supplement to WHO TRS No. 961, Annex 9 Technical supplement to WHO TRS No. 961, Annex 9/ Supplement 12

(Feat. PIC/s GDP, PE011-1)

Reference for GDP Guideline on Transport Temperature
運輸溫度之GDP法規及參考文件參照表

Item	Chapter	Description	Reference
第 9 章	運輸		
	9.4.7	**應有系統可管制保冷劑的重複使用**，確保不會誤用到未完全冷卻的保冷劑。冷凍保冷劑及冷藏保冷劑應有適當的實體隔離。	WHO TRS No. 961, Annex 9 Sec. 6, Transport and delivery Technical supplement to WHO TRS No. 961, Annex 9 Technical supplement to WHO TRS No. 961, Annex 9/ Supplement 12
	9.4.8	**應有書面程序**說明溫度敏感產品之運送流程及季節性溫度變化的管制。	WHO TRS No. 961, Annex 9 Sec. 6, Transport and delivery Technical supplement to WHO TRS No. 961, Annex 9 Technical supplement to WHO TRS No. 961, Annex 9/ Supplement 12

(Feat. PIC/s GDP, PE011-1)

藥品GDP倉儲溫控管理要點

運輸作業溫控要點基礎要求

Temperature-controlled Transport 運輸溫度控制

1. **Air and sea transport 空運及海運**
   - Ensure that any carrier contracted to transport TTSPPs by air or by sea operates under the terms of a formal **service level agreement (SLA)** drawn up between the parties.
   - The carrier is to be made responsible for maintaining load temperatures within the transport temperature profile defined for each product
   - **Temperature control in vehicles operated by a common carrier must be qualified** and the details and responsibilities for this process should be set out in a formal SLA drawn up between the parties
2. **Temperature-controlled road vehicles generally 溫控車**
   - Capable of maintaining the temperature range defined by the system set points over the full annual ambient temperature range experienced over known **distribution routes** and **when the vehicle is in motion, or parked with the main engine stopped**
   - Equipped with calibrated temperature monitoring devices with sensors located at points resenting temperature extremes(worst case)
   - Equipped with alarms to alert the driver in the event of temperature excursions and/or refrigeration until failure
   - Regularly calibrated and maintained and records kept to demonstrate compliance

(Feat. WHO TRS No. 961, Annex 9)

Temperature and Humidity Control and Monitoring during Transit 轉運間之溫度及濕度控制及監視

1. **Temperature control in temperature-controlled road vehicles 溫控車之溫度控制**
   - System able continuously to maintain air temperatures within the set point limits through the validated storage volume
   - Control sensors accurate to **+/- 0.5 °C or better**
   - Control sensors shall be calibrated
   - Control sensors positioned at the **"hot" and "cold" spots** determined by temperature mapping, even if affected by door opening
   - **Control sensors independent of the temperature monitoring system**
2. **Temperature monitoring in temperature-controlled road vehicles 溫控車之溫度監視**
   - Monitoring sensors accurate to **+/- 0.5 °C**
   - Monitoring sensors shall be calibrated
   - **Monitoring sensors positioned so as to monitor worst-case positions**
   - Provide a temperature record with a minimum recording frequency of **"six times per hour"** for each sensor position

(Feat. WHO TRS No. 961, Annex 9)

Temperature and Humidity Control and Monitoring during Transit 轉運間之溫度及濕度控制及監視

3. **Humidity monitoring in temperature-controlled road vehicles 溫控車之濕度監視制**
   - Sensors accurate to **+/- 5 % RH**
   - Sensors shall be calibrated
   - Sensors located to monitor **worst-case humidity levels** within the qualified storage volume
   - Sensors positioned so as to be minimally affected by transient events such as door opening
   - Provides a humidity record with a minimum recording frequency of **“six times per hour”** for each sensor position
4. **Temperature monitoring in passive and active shipping containers**

   主動及被動式保溫箱之溫度監視
   - **Use chemical or electronic freeze indicators, electronic loggers (with or without) and/or other suitable indicators to monitor temperature and/or humidity exposure during internal distribution**
   - Preferably use these devices for external distribution
   - **Monitor and document indicator status upon arrival**

(Feat. WHO TRS No. 961, Annex 9)

Calibration and Verification of Transport Monitoring Devices 運輸監視儀器之校正及確認

1. **Calibration of transport temperature control devices 運輸溫度控制儀器之校正**
   - Calibrate devices against a certified, traceable reference standard **"at least once a year"**
2. **Calibration of transport temperature monitoring devices 運輸溫度監視儀器之校正**
   - Calibrate devices against a certified, traceable reference standard **"at least once a year"**
3. **Calibration of transport humidity monitoring devices 運輸濕度監視儀器之校正**
   - Calibrate devices against a certified, traceable reference standard **"at least once a year"**
4. **Verification of transport alarm equipment 運輸警示儀器之確認**
   - Check functionality of temperature and humidity alarms at the designated set points
   - Check functionality of security alarm systems
   - Carry out these checks **"at least once every six months"**
   - Maintain records to demonstrate compliance

(Feat. WHO TRS No. 961, Annex 9)

Shipping Containers 運輸容器

1. **Container selection generally 容器之選擇**
   - Comply with applicable national and international standards relevant to the product type and the chosen transport route and modes
   - Protect the product being transported against mechanical damage and the anticipated ambient temperature range that will be encountered in transit
2. **Qualification of insulated passive containers 被動式保溫容器之驗證**
   - **Qualify insulated passive containers**, including any and all necessary ancillary packaging such as temperature stabilizing medium, dry ice, ice or gel packs, cool water packs or warm packs, phase change materials, partitions, bubble wrap and dunnage
   - Ensure that the qualified packaging system is capable of maintaining the TTSPPs within the temperature range needed to meet the product stability profile as stated by the product manufacturer
   - **Container qualification should include full details of the packaging assembly, the thermal conditioning regime and the minimum and maximum shipping volume, weight and thermal mass that can safely be accommodated in the container**
   - Qualification should also include the correct placement of temperature monitors where there used

(Feat. WHO TRS No. 961, Annex 9)

Shipping Containers 運輸容器

3. **Qualification of active containers**
   - Ensure that the container is capable of maintaining the TTSPPs within the temperature range needed to meet the product stability profile as stated by the product manufacturer
   - Take account of the transport route and of the anticipated ambient temperature profile over the duration of transport, measured from the point of arrival in the recipient's temperature-controlled store
4. **Product handling during packing and transport**
   - Take precautions against spillage or breakage, contamination and cross-contamination
   - Deliver TTSPPs to outside recipients by the most suitable mode pf transport available in order to minimize delivery time
5. **Cleaning road vehicles and transport containers**
   - Ensure that all internal surfaces of load compartments are regularly cleaned
   - Do not allow the accumulation of duct, dirt and waste, including packaging waste in load compartment, or in reusable shipping container
   - Do nor allow accumulation of frost and ice in refrigerated vehicles, particularly ice contamination by spillages

(Feat. WHO TRS No. 961, Annex 9)

藥品GDP倉儲溫控管理要點

運輸車之驗證及確效

Technical Supplement: Qualification of Temp-Controlled Vehicles 溫控車之驗證

1.2.2 Validation

Once the vehicle has been delivered it is essential that its actual performance is validated. Validation is used to demonstrate that the specified performance standards are met in the actual operating environment. This process should take place before the vehicle is used to transport valuable TTSPPs.

Validation procedures are increasingly being seen as a requirement of cGMP (current Good Manufacturing Practice). The validation process applies a set of clearly defined criteria and provides documented evidence that the equipment is fit for its intended purpose. Typically this is a three stage exercise:

Installation Qualification (IQ) - verifies that the equipment is installed correctly as per the original requirements and that any documentation needed for its use is in place.

Operational Qualification (OQ) - verifies that of the equipment concerned with maintaining and ensuring product quality operate correctly over all expected ambient conditions.

Performance Qualification (PQ) - verifies that those parts of the equipment concerned with maintaining and ensuring product quality can perform as intended in an effective and repeatable manner over time.

Technical Supplement: Qualification of Temp-Controlled Vehicles 溫控車之驗證

1.2.2 確效

- 當車輛出廠時，基本上此車輛已經通過性能驗證
- 確效的目的是為了展現車輛在實際的作業環境下，能夠符合某些特定的性能標準要求。因此確效必須在車輛實際載運溫度敏感產品(冷鏈產品) 之前完成確效作業
- 確效作業已經被視為 cGMP的要求。其藉由明訂的標準和書面證據來證明設備符合預期的使用目的。 通常包括三個階段驗證:
- 安裝驗證 (Installation Qualification - IQ) – 確認設備已經依照原來的需求正確地安裝，而且操作所需的各項文件也都已經備齊。
- 操作驗證 (Operational Qualification - OQ) – 確認那些維持以及確保產品品質無誤的設備，可以在所有預期的環境條件下操作
- 性能驗證 (Performance Qualification - PQ) – 確認那些維持以及確保產品品質無誤的設備配件可以有效且重複不斷地達成其預期目的

WHO TRS 961 Annex 9 Model guidance for the storage and transport TTSPPs

6.6 Qualification of temperature-controlled road vehicles

Where temperature-controlled vehicles are directly owned and/or operated, qualify each vehicle before it becomes operational, wherever possible. The qualification procedure should:

- demonstrate that the air temperature distribution is maintained within the limits specified throughout the temperature-controlled compartment for both air and product temperatures for commonly used load layouts and at the ambient temperature extremes anticipated during normal operation over known routes;
- demonstrate the humidity distribution throughout the temperature-controlled compartment for commonly used load layouts, where products are being transported that require a humidity-controlled environment;
- define zones within the vehicle's payload area which should not be packed with TTSPPs (for example areas in close proximity to cooling coils or cold air streams);
- demonstrate the time taken for temperatures to exceed the designated maximum in the event that the temperature-controlling unit fails; and
- document the qualification exercise.

An alternative approach is to perform an initial full qualification on each trailer/refrigeration unit type combined with an installation qualification (IQ) for each example when a new vehicle becomes operational.

Carry out additional qualification exercises whenever significant modifications are made to the vehicle. Consider the need for requalification whenever temperature and/or humidity monitoring shows unexplained variability that is greater than normal.

WHO TRS 961 Annex 9 Model guidance for the storage and transport TTSPPs

6.6 溫控車輛的驗證

可能的話，每一部溫控車輛在使用之前應驗證。驗證的程序包括：

- 證明在一般的裝載下，正常的路線範圍可能面臨的最差環境條件下，車輛溫控的空間內，其空氣溫度分布應能維持在特定的規格內。
- 對於載運需要濕度管制的產品，展現一般的裝載情況下，溫控車廂內的溼度分布情況。
- 找出溫控車廂內部不可以放置溫度敏感產品的區域。(例如冷氣直吹的位置)
- 確認當設備失去功能時，車廂可以保溫的期間時效。
- 文件化(紀錄)驗證活動。

另一個可行的方式是，當新車服役前，依照車廂/冷藏空調的機型分類執行代表車輛的完整驗證，與其 IQ驗證。

再驗證時機：

- 當車輛有重大的改裝維修，應該執行再驗證。
- 當溫度 及/或 濕度產生比以往更大的偏差，卻無法合理解釋時，應該再驗證。

Qualification of Vehicles 車輛驗證

安裝驗證

1. 車輛資訊
   - 一般性能需求 (車輛製造廠、年份、載重噸數、車廂內部尺寸)
   - 控溫性能需求 (空調機型、車廂隔熱材質與厚度)
2. 確認溫控配件安裝妥當
3. 車輛使用手冊、保養紀錄等

操作驗證

1. 確認空調機功能可以達到需要的溫度
2. 需要的降溫冷卻時間
3. 確認車廂的保溫時間

性能驗證

1. 依照最差條件
   - 最複雜的運送模式
   - 各路線貨車一天最久的行駛時間、最久停車時間
   - 最頻繁的引擎熄火次數
   - 夏天最熱的送貨地區
2. 測試**最高載貨量(旺季爆量)**的車廂溫度分布
3. 找出車廂內部的最差位置
4. 確認是否有禁止放貨的位置

(Feat. Technical supplement to WHO TRS No. 961, 2011)

Validation of Cold Chain Products 冷鏈產品之確效

溫度計的校正標準

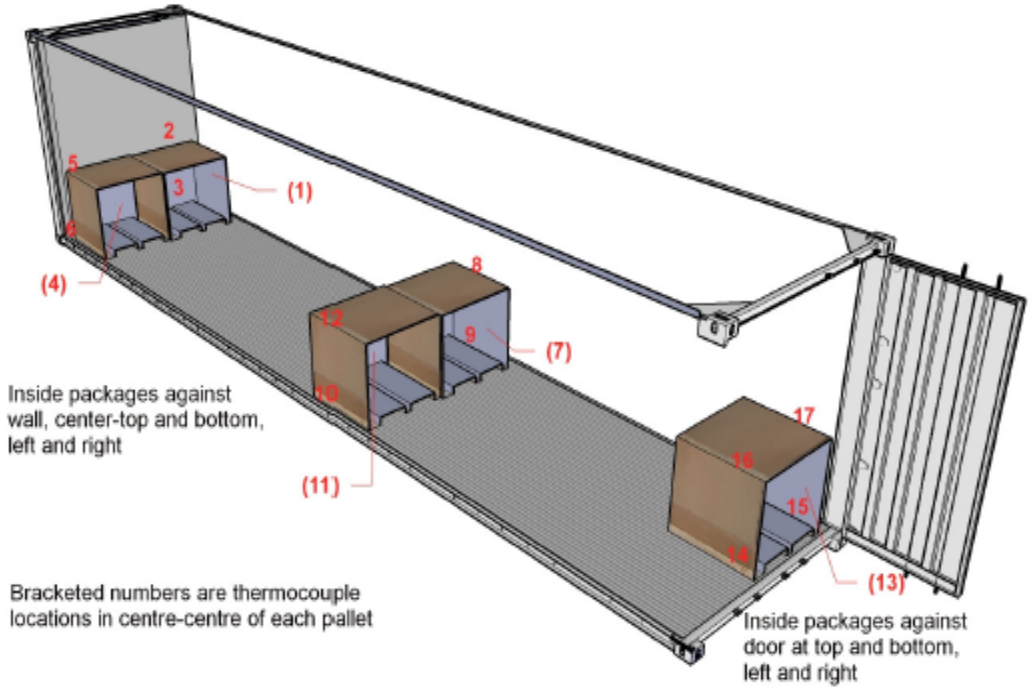
依據 WHO 標準，溫度計校正的允收規格應該是 +/- 0.5 °C

溫控需求標準

1. 必須符合標示的儲存溫度(例如:冷鏈產品規格2~8 °C, 代表低溫不得低過 2-0.5 °C, 高溫不得高過 8+0.5 °C)
2. 如果以車輛載運但是沒有使用保冷箱 – 車廂溫度必須在運送期間保持 2~8 °C
3. 如果使用保冷箱 –保冷箱溫度在運送期間能夠保持 2~8 °C，不論運輸過程是以車輛或飛機載運

Location of Temperature-Monitoring Devices for Mapping of Loaded Trailer

Figure A1.1 - Example layout for monitoring a part loaded trailer



Source: Cambridge Refrigeration Technologies

1. 溫度計放在包裝箱裡面
2. 佈點在最容易受到影響的地方
3. 如果有多個到貨地點，最後一箱應該有溫度計

Qualification of temperature controlled road vehicles -Technical supplement to WHO Technical Report Series, No. 961, 2011

Qualification of Mock Loading test 模擬負載測試之驗證

1. 一般而言，用來裝載溫控品的”設備” 必須先用極端的高低溫測試過，但因為很難找到大型的恆溫室來進行模擬測試，因此使用真正的道路測試是可以接受的折衷方式。
2. 執行道路測試時，可以使用
   - 代用品 – 過期的產品或者類似材質的其他產品
   - 真正的產品 – 如果過去已經先有配送行為，現在才開始有確效的情況下 (但是真正的產品不可以用在 保溫和降溫測試，因為產品會暴露在極端的溫度)
3. 最低裝載 – 不是空車(因為實務上車輛就是要載貨)。但有可能為了一箱貨品派一部專車，此時一箱貨品就是最低裝載量。
4. 最高裝載 – 模擬旺季爆量時的滿載情況 。

Monitoring of Transportation 運輸之監視

1. 例行監控車輛溫度
2. 定期校正溫度計
3. 定期檢視維修保養紀錄
4. 抽檢車輛裝載
5. 異常報告
6. 再驗證

藥品GDP倉儲溫控管理要點

運輸之模式

After Qualification 驗證後

- 即便在國內運輸，仍然需要考慮 海運、空運與陸運對溫控產品的影響
- 特別是多種運輸模式組合而成的運輸路線

(102年藥品GDP主題論壇(二)

Model of Transportation 運輸之模式

海運

- 運輸時間較長
- 應用於國際大貨量、國內離島之運輸
- 藥廠 – 陸運 – 港口 – 海運 – 港口 - 陸運 – 倉庫 – 陸運 – 醫院

空運

- 運輸時間較短
- 應用於國際、國內離島之小貨量運輸
- 藥廠 – 陸運 – 機場 – 空運 – 機場 - 陸運 – 倉庫 – 陸運 – 醫院

陸運

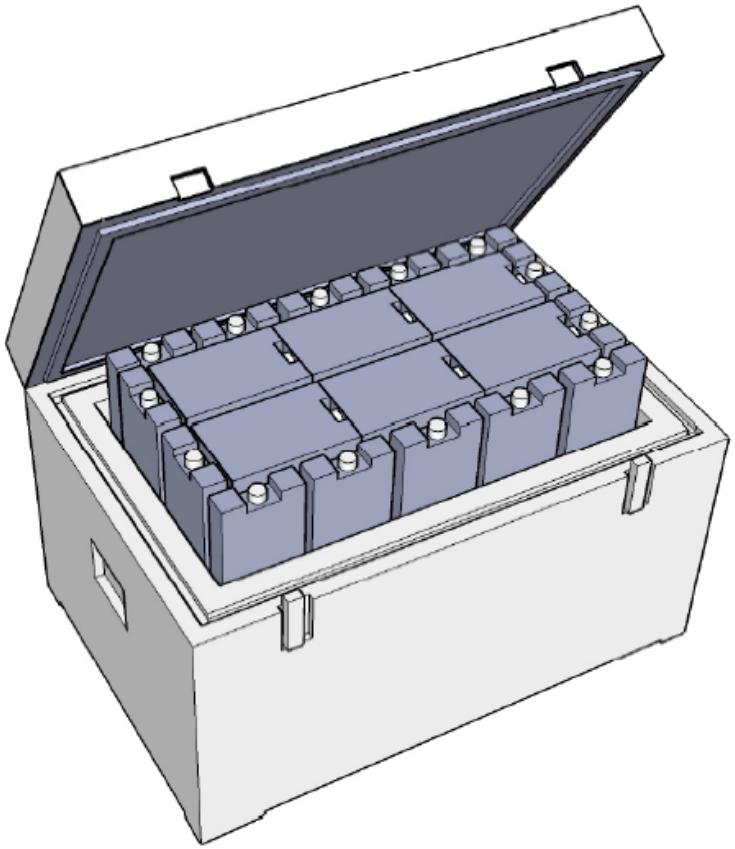
- 運輸時間依照目的地而定
- 應用於台灣島內運輸、或是國際路陸之運輸
- 藥廠 – 陸運 – 倉庫 – 陸運 – 醫院

運輸途徑越複雜，造成溫度偏差的風險越高

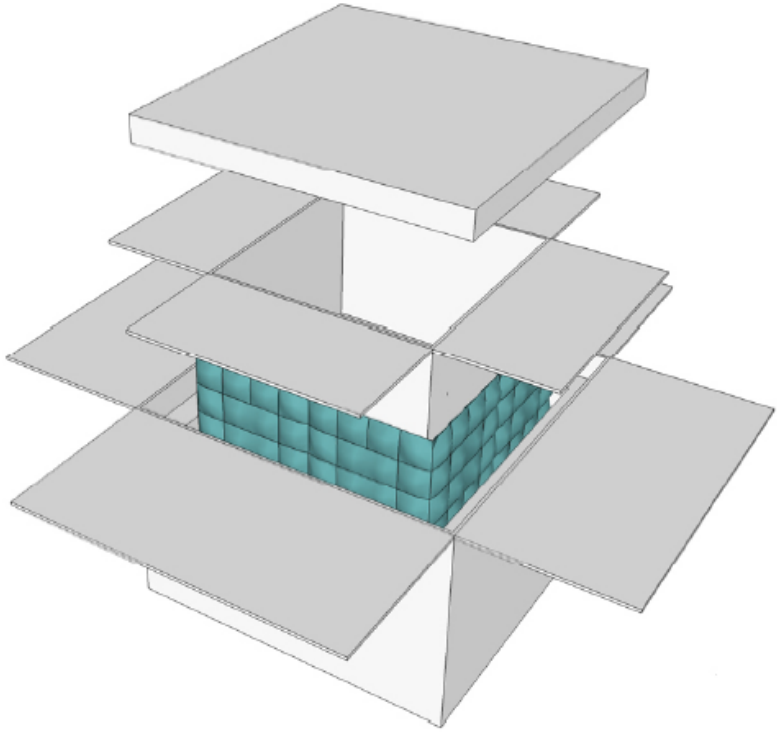
(102年藥品GDP主題論壇(二)

Various Packaging for Temp-Controlled Product Delivery
溫控運送包裝形式

Generic passive containers with coolant packs



Reusable container

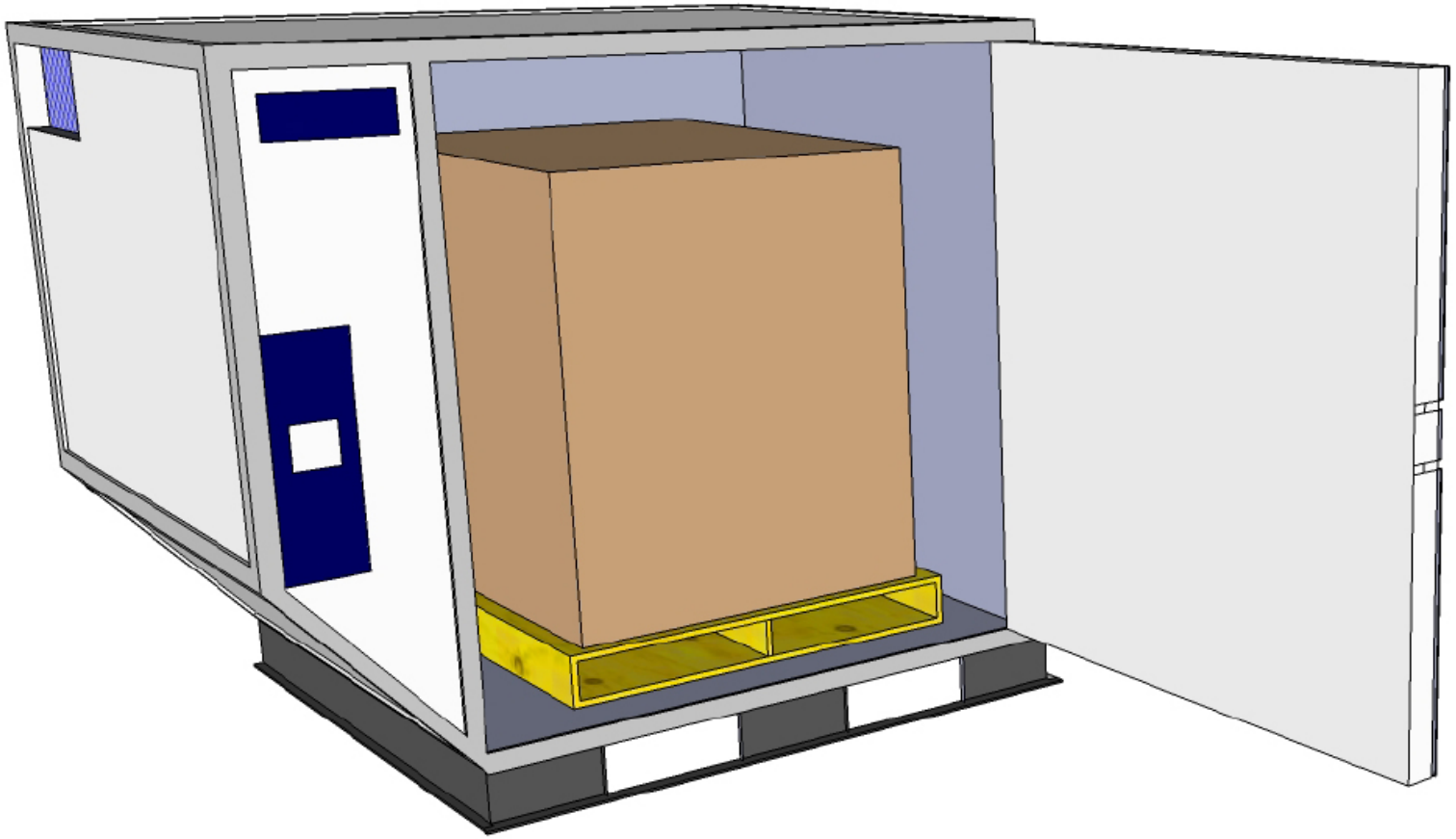


Disposable insulated carton

(Feat. Technical supplement to WHO TRS No. 961, Annex 9)

Various Packaging for Temp-Controlled Product Delivery
溫控運送包裝形式

Active air transport container – type LD3



(Feat. Technical supplement to WHO TRS No. 961, Annex 9)

Various Packaging for Temp-Controlled Product Delivery
溫控運送包裝形式

- 整板包裝(不加冰寶)常用於國際運輸的船運冷藏貨櫃 或者空運的主動式冷藏櫃 (例如：Environtainer, Safe..)
- 主動式冷藏櫃(充電電池或乾冰)可多次使用。

- 國際運輸也常見整板藥品用冰寶包裝載運到目的地。
- 此款式為被動式低溫裝置（依靠冰寶）
- 單次使用。

- 保麗龍保冷箱常見於小貨量的載運
- 保麗龍箱內部需要冰寶保持箱內的低溫。
- 容易破損，不利於多次使用。

- 塑膠硬殼式的保冷箱用於小貨量的載運。
- 需要冰寶保持箱內低溫。
- 材質堅硬利於多次使用。

(102年藥品GDP主題論壇(二)

Transport Operations by Sea 海運作業

- 海運階段需克服的困難：
  - 外在環境的溫差
  - 運輸時間較長
- 國際運輸可以應用 Cold Container (需插電)，貨量少時可能會併櫃。
- 國內離島可以使用 保冷箱。
- 抵達目的機場/港口後，冷藏貨櫃可以用貨車載運到目的倉庫。

(102年藥品GDP主題論壇(二)

Transport Operations by Air (Active temperature container)
空運運輸作業(主動式溫控容器)

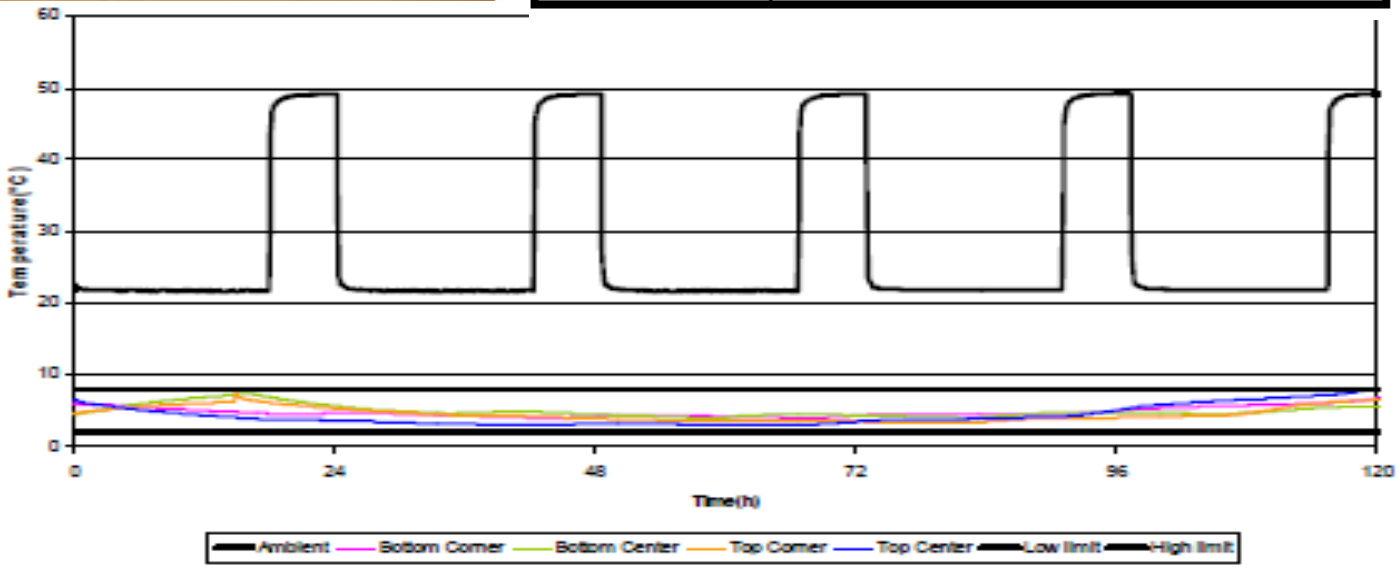
- 空運階段需克服的困難：外在環境的溫差(停機坪)、載運貨品限制 (例如：乾冰)、天候問題航班停飛 (霧季、颱風)
- 可以應用active temperature controlled container (i.e. Envirotainer ®, Safe ®) 作為國際空運之溫控裝置。或是保冷箱作為國內(含離島)之運輸。
- 抵達目的機場/港口後，可以用貨車載運到目的倉庫。

(102年藥品GDP主題論壇(二)

Transport Operations by Air (Passive Temperature Maintained Package) 空運運輸作業(被動式溫控容器)

RePak 120 - Basic Specifications	
Temperature and Time range	Holds 2°-8°C for up to 120 hours (performance data available on request)
Outside Dimensions	48" x 40" x 41.75" (inc pallet)
Interior Capacities	32" x 24" x 25" Up to 140 lbs payload
Weight (empty)	177 lbs (without pallet) approx
Stacking Capacity	4 high (empty); 2-3 high (depending on payload)
Other options	Plastic pallet; re-usable outer covering

Summer



圖片擷取自網路

(102年藥品GDP主題論壇(二)

Environment and Transportation of Removed Islands
離島之環境及運輸

1. 離島航線並非專用貨機，而是客機的貨艙兼放藥品。
2. 航空站提貨並沒有空調。
3. 以上，不論是 Active Container or Passive package, 離島航線都無法承運包裝好的整棧板貨量。
4. 現行的運輸作法是 使用小型的 passive insulated box 包裝後，化整為零塞在貨艙載運到離島

空運貨品裝貨過程 (擷取自網路)

金門機場貨運站 (擷取自網路)

(102年藥品GDP主題論壇(二)

Environment of Transport Operations by Air
空運之環境及運輸作業

1. 國際航線的貨機可以容納整板包裝的溫控產品，因此可以使用主動式的包溫包裝或是被動式的保溫包裝
2. 國際航線的運輸時間比離島航線的時間久長，因此整板包裝貨品時，溫度計將隨貨一起放置在保溫包裝內以監視全程的溫度。
3. 主動式與被動式包裝的貨品到倉庫時，其卸貨與進倉的步驟應考慮是否會造成溫度偏差。

空運貨品裝貨過程 (擷取自網路)

Transport Operations by Road 陸運之運輸作業

圖片擷取自網路

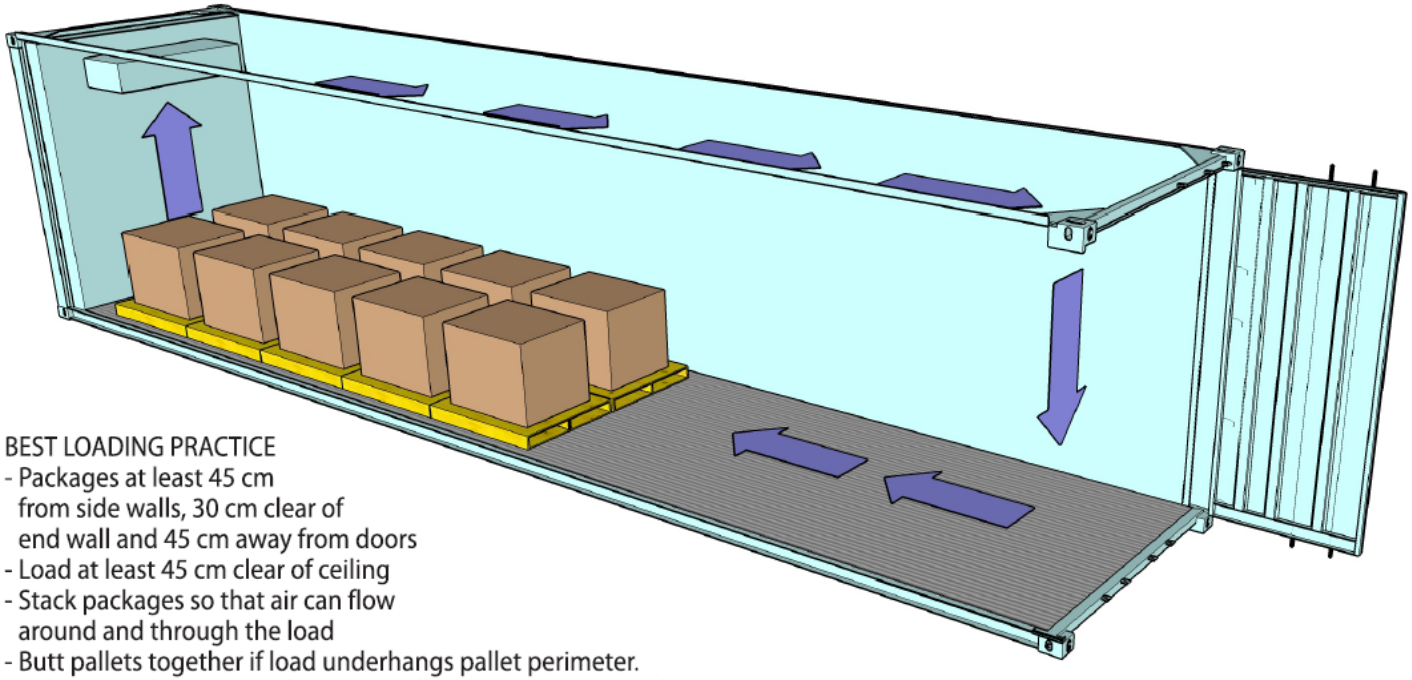
- 陸運可為下列目的之應用
  - 歐陸國際間的運輸
  - 國內陸路運輸
  - 接駁機場/港口與起運站和目的地的運輸
- 可以使用溫控車輛載運大量貨品，或者保溫箱載運小貨量保溫藥品。
- 面臨的挑戰：溫控車熄火停車 (特別是歐陸長途的載運)

(102年藥品GDP主題論壇(二)

Packing a Refrigerated Vehicles 冷藏車之裝載作業

Packing a refrigerated vehicle

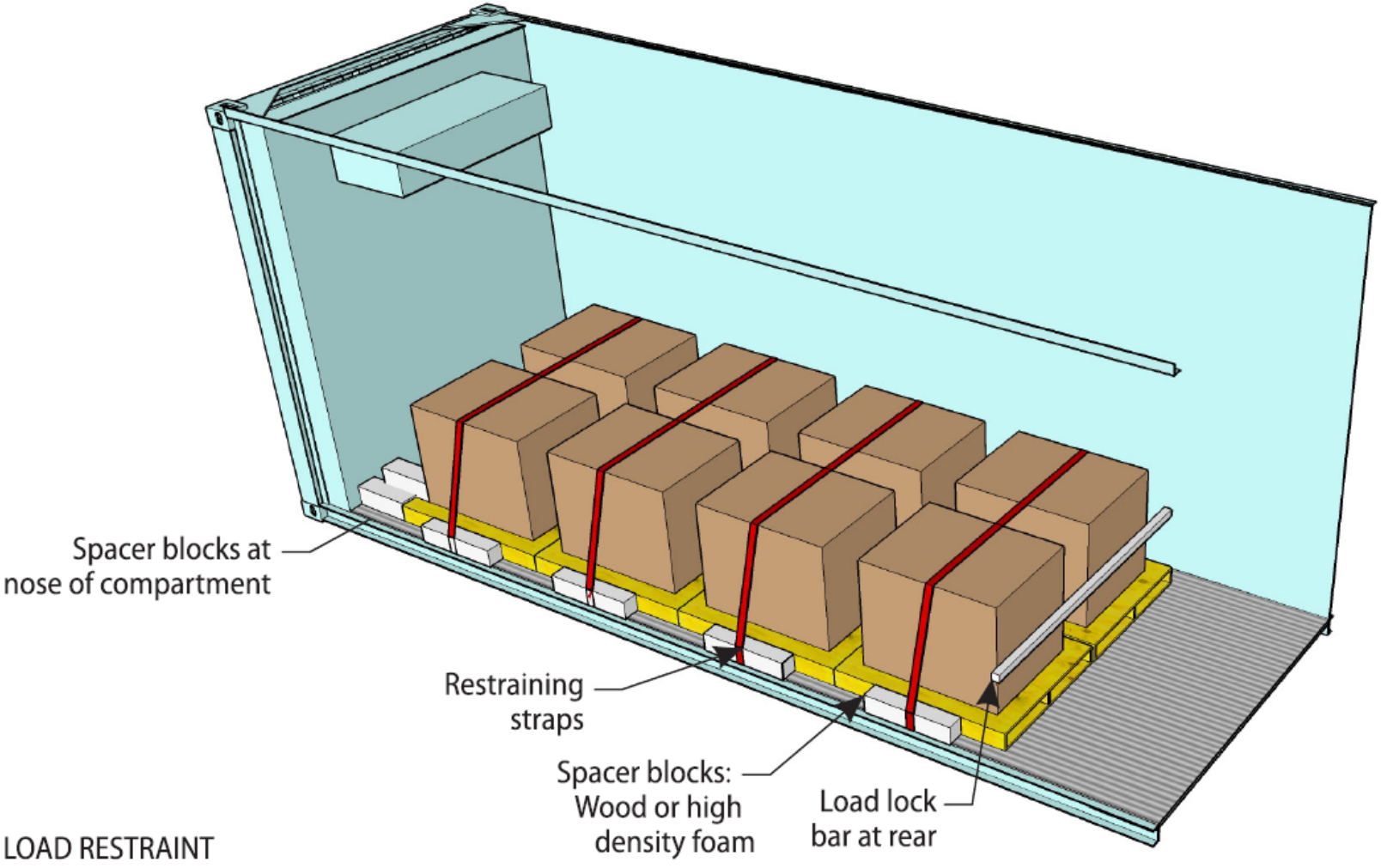
The following diagrams show the correct procedure for packing pallets in a refrigerated vehicle.



BEST LOADING PRACTICE
- Packages at least 45 cm from side walls, 30 cm clear of end wall and 45 cm away from doors
- Load at least 45 cm clear of ceiling
- Stack packages so that air can flow around and through the load
- Butt pallets together if load underhangs pallet perimeter. Otherwise place spacers between pallets to ensure air circulation
- Place pallets with boards running front to back to promote airflow under load
- Remove debris that may block airflow

(Feat. Technical supplement to WHO TRS No. 961, Annex 9)

Packing a Refrigerated Vehicles 冷藏車之裝載作業



(Feat. Technical supplement to WHO TRS No. 961, Annex 9)

Validation of Temp-Controlled Box 保溫箱之確效

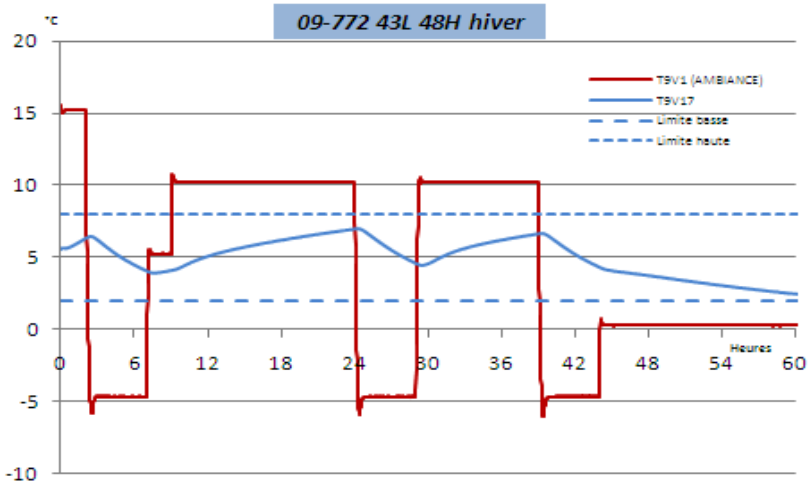
Ex-Temp	Internal Dimensions		External Dimensions		Gross		Volumetric		T-500
model	cm	in	cm	in	kg	lb	kg	lb	GelPaks
20	20x20x20	7.9x7.9x7.9	32x32x36	12.6x12.6x14.2	1.70	3.74	6.00	13.20	6
30	30x30x30	11.8x11.8x11.8	42x42x46	16.5x16.5x18.1	2.40	5.28	13.50	29.70	16
3040	40x30x40	15.5x11.8x15.5	52x42x56	20.5x16.5x22.0	3.90	8.58	20.00	44.00	24
45	45x45x45	17.7x17.7x17.7	57x47x58	22.5x18.5x22.8	5.90	12.98	31.50	69.30	40
Half-Pallet Cool	60x40x58	23.6x15.5x22.8	81x61x70	31.9x24.0x27.6	12.50	27.50	69.00	151.80	18
Half Pallet Freeze	68x48x58	26.8x18.9x22.8	81x61x70	31.9x24.0x27.6	12.50	27.50	69.00	151.80	n/a

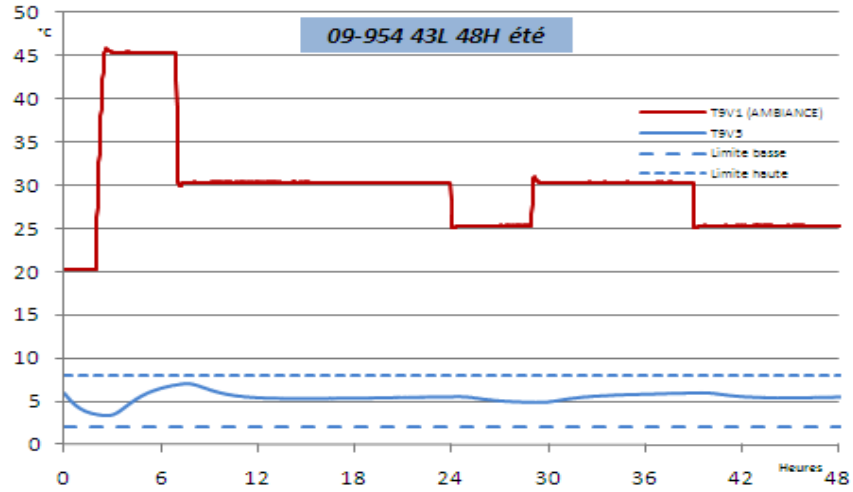
1. 先收集箱子(包括配件如冷卻包、緩衝材料、紙箱....等等)的所有資訊，資訊包括 物質安全資料、規格(尺寸、重量) 以及使用的數量
2. 決定如何包裝 (冷卻包和其他配件之間的相關位置)
3. 決定要放多少顆溫度計做溫度測繪
4. 決定怎樣的條件算合格
5. 寫成 IQ Protocol

(102年藥品GDP主題論壇(二)

Validation of Temp-Controlled Box 保溫箱之確效

1. 將模擬藥品(可以用瓶裝水或瓶裝粉末)和保冷箱以及配件等依照設計的條件預冷，例如先在冰箱冰幾天，或是冰寶需冷凍幾天。
2. 依照設計的包裝方式將模擬藥品放入保冷箱並掛上溫度計(滿箱)
3. 依照設計的包裝方式將空紙箱(不放模擬藥品) 放入保冷箱中, 並掛上溫度計 (空箱)
4. 找一個最熱的環境 模擬停機坪或沒有空調的車廂溫度，測試模擬環境下，滿箱和空箱的溫度變化
5. 最冷的環境模擬冬天寒流來襲的溫度，測試滿箱和空箱的溫度變化
6. 決定合格標準(例如: 2-8 ºC 可以維持多久時間)
7. 寫成 OQ Protocol 和 Report





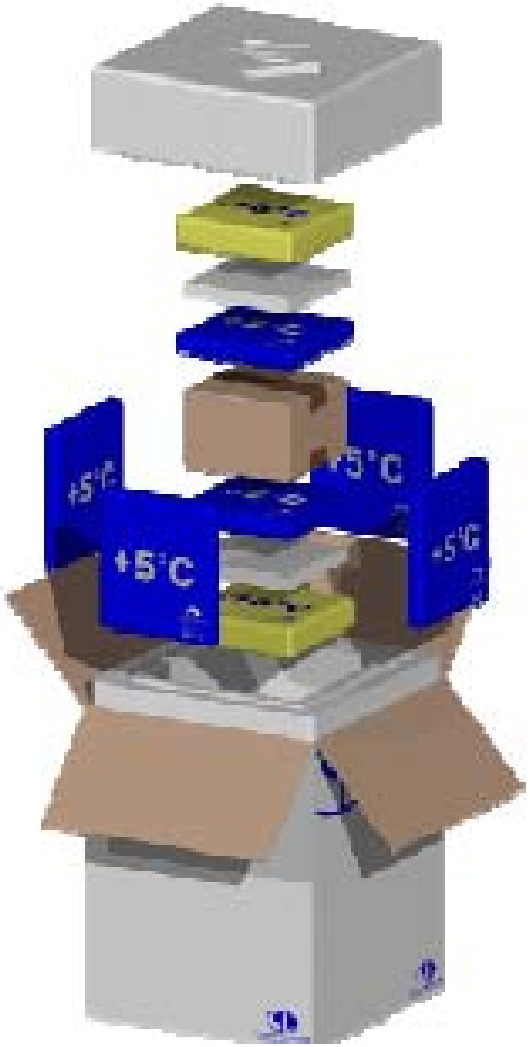
(102年藥品GDP主題論壇(二)

Validation of Temp-Controlled Box 保溫箱之確效

決定路線：

1. 設想最糟的狀況例如：
   - 時間 – 送到客戶端才發現訂單錯誤只好送回倉庫, 這段時間要多久? 保冷箱是否能撐得住?
   - 地理位置 – 夏天的台東是台灣最熱的地方，保冷箱撐得住嗎? 如果送去又退回，保冷箱撐得住嗎?
   - 最複雜的旅程 – 除了陸運之外，如果有使用空運的旅程就要測試空運的路線
   - 不同的氣候 – 夏天和冬天的大環境溫差也要分別測試
2. 設計幾條測試路線，路線的總和必須測試到上面的幾個考量點
   - 地理位置 – 送到台東，開箱假裝驗貨，再包裝好送回來
   - 複雜的旅程 – 送到馬祖 (陸運和空運的組合) 開箱假裝驗收，再送回來, 或者送到金門 (陸運+海運的組合)
   - 夏天冬天都要實地測試
3. 決定合格的標準
   - 時間：實際運送時，最複雜旅程所需要的時間和路程最遠客戶的時間相比，哪一個需要比較多的時間，那個時間就是合格標準
   - 溫度：內部溫度都要在 2-8 °C之間
4. 設想好之後，寫成 protocol，測試，再寫成報告

Key Points of Validation on Temp-Controlled Box
保溫箱之確效要點



- IQ – 箱子、冰寶和其他配件的規格與檢查、物質安全資料表、材質證明、組合方式.....
- OQ – 冰寶與箱子(含配件)的預冷條件和時間，在極端環境下測試空載與滿載
- PQ – 實際配送測試，應考慮季節因素、地理位置、運送時間(含拒收)以及 Mode of Transportation等。擬定路線測試。
- 再確效 – 沒有重大變更情況下，也要定期再確效箱子與冰寶的溫控能力。
- 保冷箱和冰寶應有進貨檢查機制，確保每次採購的品質都符合規格
- 若回收保冷箱重複使用，應該有清潔程序並制定使用年限的判定準則。
- 載運cold chain 藥品時，請不要回收使用”不明規格”的冰寶，例如國際運輸整板 Passive container 附帶的冰寶，因為不清楚其預冷條件、也不確定其規格，可能會造成運送途中不可預期的溫度偏差。

(102年藥品GDP主題論壇(二)

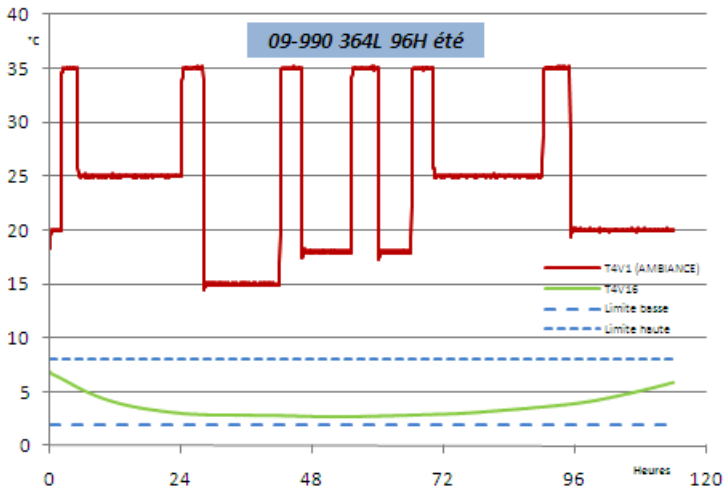
Requirement of Validating Temp-Controlled Product
溫控產品確效需求

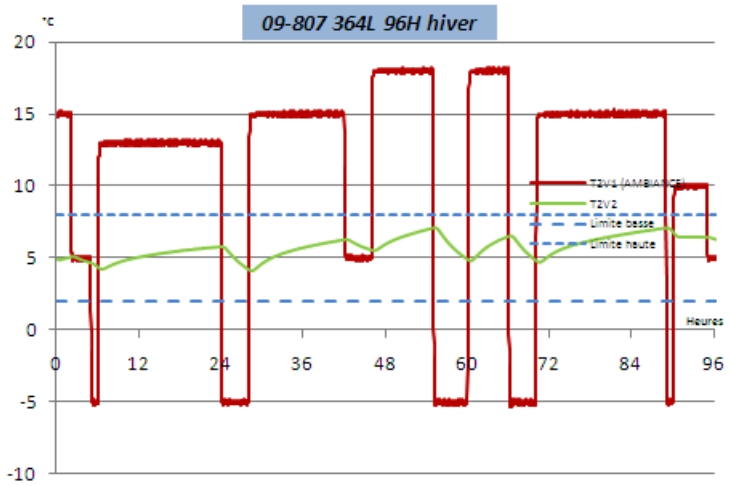
- 批發運銷商應確認何種關鍵設備驗證及/或關鍵流程確效是必須的，以確保其安裝及操作的正確性。
- 該驗證及/或確效作業(例如儲存、揀貨及包裝流程)之範圍及程度應以文件化的風險評估方式測定。
- 設備與流程在開始使用前以及有**重大變更**(如：維修及維護)應分別驗證及/或確效
- 對於溫度敏感的產品，應使用經驗證的設備(例如保溫包裝、溫控裝存箱櫃或溫控車)以確保產品在製造商、批發運銷商及客戶間運送時，維持在正確的運輸條件。
- 溫控車在運送時所使用的溫度監測設備應定期進行維護及校正。應執行代表性條件下的溫度測繪，且考量到季節變化(必要時)。
- 在隔熱箱使用冷卻包時，須放在不會與產品直接接觸之處。員工必須接受組裝隔熱箱(季節性配置)及重複使用冷卻包程序之訓練。
- 應有系統可管制重複使用冷卻包，確保不會誤用到不完整的冷卻包。
- 冷凍冷卻包及冷藏冷卻包應有實體隔離。

(102年藥品GDP主題論壇(二)

Temperature Monitoring – Transport Operations
溫度監視-運輸作業

- 應例行監視 Cold box / package 的環境溫度
- 應例行監視 Validated Cold Box 的內部溫度





(102年藥品GDP主題論壇(二)

平均動力溫度

Edwards

平均動力溫度

平均動力溫度之定義及計算

Definition of Mean Kinetic Temperature
平均動力溫度之定義

- **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 temperature.**

- MKT may be considered as an isothermal storage temperature that simulates the non-isothermal effects of storage temperature variation. It is not a single arithmetic mean.

- The temperatures used for calculating MKT can be conveniently collected using electronic devices that measure temperatures at frequent intervals **(e.g. every 15 minutes)**.

- MKT can be calculated directly or the data can be downloaded to a computer for process. Software to compute the MKT is available commercially.

(Feat. USP, 1079)

Calculation of Mean Kinetic Temperature
平均動力溫度之計算

- **MKT is calculated by the following equation:**

$$T_k = \frac{\Delta H/R}{-ln\left(\frac{e^{-\Delta H/RT_1} + e^{-\Delta H/RT_2} + \ldots + e^{-\Delta H/RT_n}}{n}\right)}$$

- T_k: the mean kinetic temperature
- ΔH: the heat of activation, 83.144 kj • mole^{-1};
- R: the universal gas constant, 8.3144 x 10^{-3} kj • mole^{-1} • degree^{-1};
- T_1: the value for the temperature recorded during the first time period, e.g. the first week;
- T_2: the value for the temperature recorded during the second time period, e.g. the second week;
- T_n: the value for the temperature recorded during the *n*th time period, e.g. *n*th week, *n* being the total number of storage temperatures recorded during the observation period.

(Feat. USP, 1079)

MKT During Storage and Distribution
儲存及運銷之平均動力溫度

- Drug products stored either in warehouse conditions or in transportation modes may experience excursion from their acceptance temperature ranges.

- One method of analysis for drug product stored outside its respective label storage conditions is the use of an MKT calculation.

- The MKT analysis may be used storage conditions that exceeded the acceptable parameters for a drug product, for a short period of time and is NOT intended to be a measure for long-term storage.

(Feat. USP, 1079)

Temperature Excursions and MKT
超溫與平均動力溫度

- **Mean Kinetic Temperature not exceed to 25°C.**

- Excursions between 15°C to 30°C that are experienced in pharmacies, hospitals, warehouses and during are allowed.

- Provided the mean kinetic temperature does not exceed to **25°C**, transients spikes to **40°C** are permitted as long as they do NOT exceed to 24 hours.

- Spikes above **25°C** may be permitted only if the manufacturer so instructs.

(Feat. USP, 659)

Stability Testing of New Drug Substances and Products
藥品之安定性試驗

- **ICH Q1A(R2)**

2.1.7.1. General case

Study	Storage condition	Minimum time period covered by data at submission
Long term*	25°C ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH	12 months
Intermediate**	30°C ± 2°C/65% RH ± 5% RH	6 months
Accelerated	40°C ± 2°C/75% RH ± 5% RH	6 months

*It is up to the applicant to decide whether long term stability studies are performed at 25 ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH.

(Feat. ICH Q1A(R2)

Q & A

Helping Patients is Our Life's Work, and *life is now*