藥品倉儲空調系統建置與溫度異常處理要點

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2018.08.22/2018.08.28/2018.09.07

空調系統建置與溫度異常處理要點

藥品倉儲空調系統　建置時會考慮

1. 倉儲大小？
2. 潔淨室 或 一般區？
3. 是否需要有回風口？

空調系統建置與溫度異常處理要點

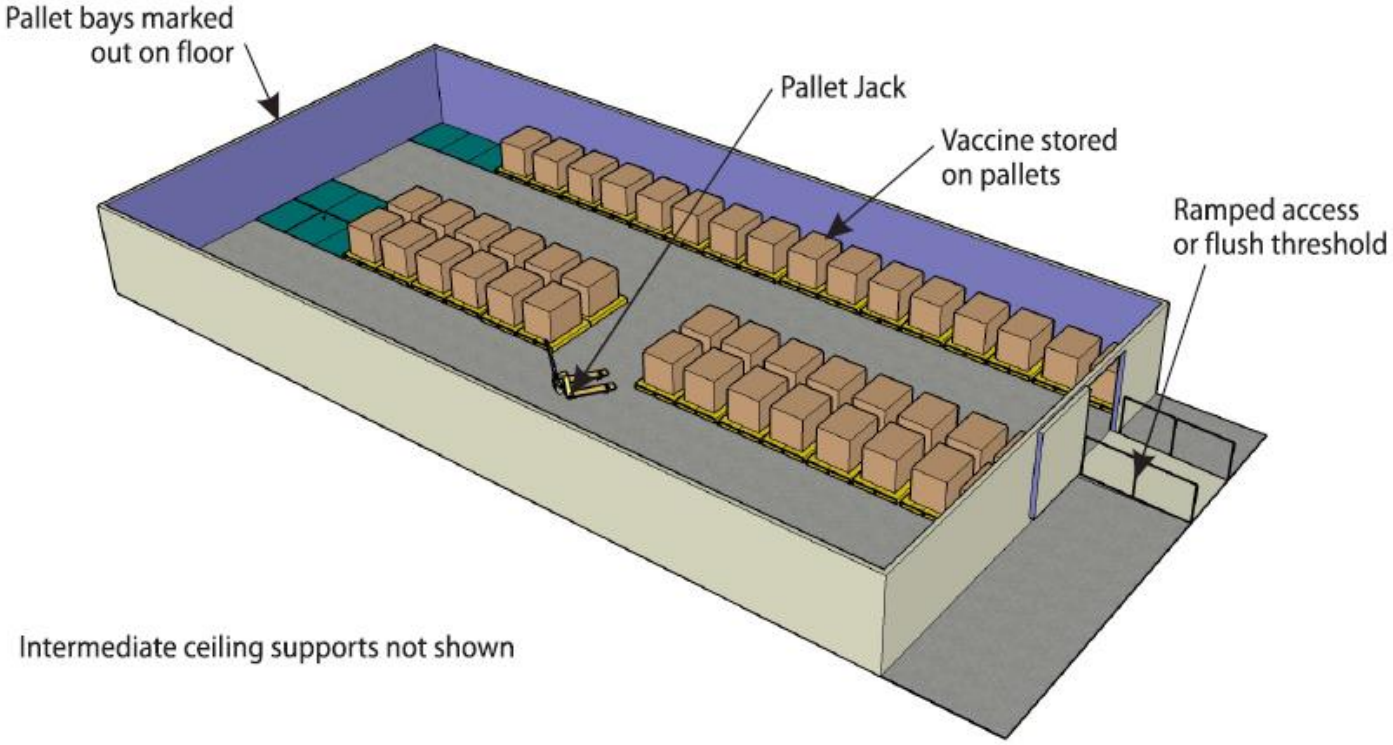
倉儲空調系統　建置時會考慮

4. 藥品擺放位置
(棧板上 或 儲架上)

5. 空氣流向
(下出風 或 側出風)

空調系統建置與溫度異常處理要點

Figure 4
Pallet standing store



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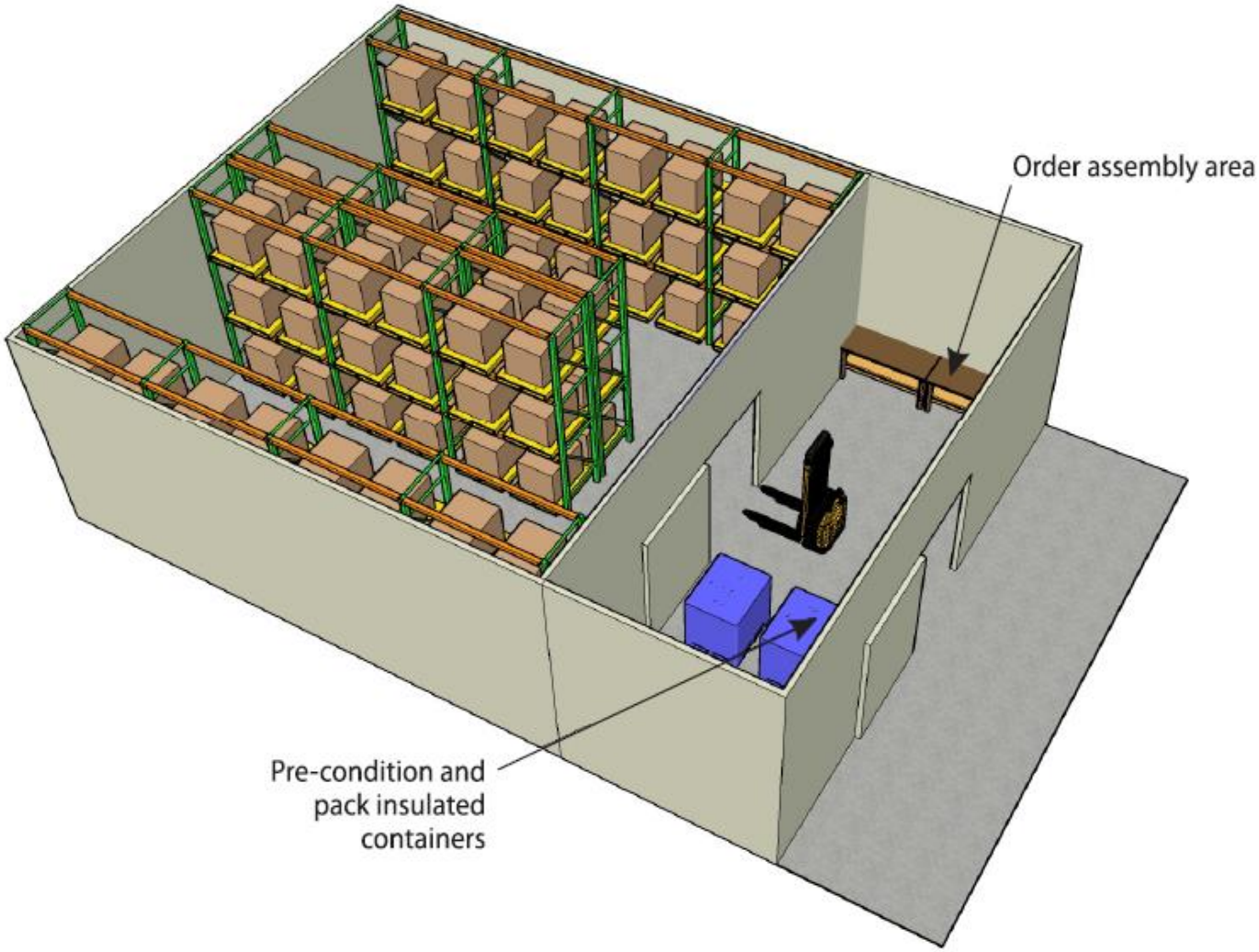

空調系統建置與溫度異常處理要點

哪些條文說了有關”倉儲溫度“？

空調系統建置與溫度異常處理要點

2.4 訓練

2.4.4 需以嚴謹條件處理之藥品，其負責人員應接受特定訓練。該類藥品，如有危害性之藥品、核醫放射性藥品、管制藥品及對溫度敏感之藥品。

空調系統建置與溫度異常處理要點

3.1 原則：藥商必須具備適當且足夠之作業場所、配備及設備，以確保能夠適當儲存及運銷藥品，此作業場所必須保持潔淨、乾燥及維持於可接受之溫度範圍內。

空調系統建置與溫度異常處理要點

藥品儲存溫度範圍：

室溫：**+15** 到**+ 25 ˚C**。

低溫：**+8** 到**+ 15 ˚C**。

冷藏：**+2** 到**+ 8 ˚C**。

冷凍：低於 **-15 ˚C**。

空調系統建置與溫度異常處理要點

3.3 溫度及環境管制：

3.3.1 應具備適當之設備及程序以確認藥品之儲存環境。需考量之環境因素包括作業場所之溫度、濕度、光線及清潔。

空調系統建置與溫度異常處理要點

3.3 溫度及環境管制：

3.3.2 儲存區應於代表性之條件下於開始使用前進行初步之溫度測繪評估。溫度監測設備應依照測繪評估結果設置，以確保監測設備為位於歷經極端溫度波動之位置。溫度測繪評估應依風險評估於有重大改變時重複執行。可視室溫作業場所大小，並執行潛在風險評估，依照其評估結果放置溫度監測器。

空調系統建置與溫度異常處理要點

3.4.5 應製作關鍵設備之維修、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之任何設備。

空調系統建置與溫度異常處理要點

6.3.3 需要特殊儲存條件（如低溫）之藥品，僅於文件證明藥品一直儲存於允許之儲存條件內，始得退回至可銷售品庫存。如有任何偏差發生，須於可證明藥 品完整性之條件下進行風險評估。其證明應涵蓋下列過程：

(1) 運送至客戶。 **(2)** 藥品之檢查。
(3) 運送包裝之拆封。
(4) 退回藥品之包裝。
(5) 收集藥品並退回給藥商。
(6) 運輸過程中之溫度紀錄。
(7) 退回運銷點之冷藏庫。

空調系統建置與溫度異常處理要點

9.1 原則：

9.1.1 藥商應確保供應藥品時防止藥品破損、摻假、竊盜，及確保於運送時維持於可接受之溫度條件下。

空調系統建置與溫度異常處理要點

9.2 運輸

9.2.2 如於運輸時發生偏差，如溫度偏離或藥品毀損，應通報藥商及受影響藥品之收貨者，且應有調查及處理溫度偏離情況之程序。

9.2.5 溫度管制需求應依運送路線之風險評估決定。運送時，於車輛及裝存箱櫃內 用於監測溫度之設備，應定期進行維護及校正。

空調系統建置與溫度異常處理要點

9.2 運輸

9.2.9 運輸如由第三方執行時，契約應包含附表七之要求，藥商應告知並確保運輸者運輸相關之所有條件。當運輸過程中有上、下貨或經轉運站時，應特別注意其儲存設施之溫度監測、清潔及安全性。

空調系統建置與溫度異常處理要點

溫度分佈驗證執行方式

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- 倉儲**Mapping**動作應定期執行 **(**至少每三年**)**

- 當有以下變更時，需執行**Re-Mapping exercise**
- **1.** 庫存數量已超出原規劃者。
- **2.** 擺放空間及位置已影響空氣流動。
- **3.** 變更冷凍設備或擺放點。
- **4.** 當監測紀錄**(**溫度或濕度**)**顯示無法預期的
- 變異。

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- 舉凡所有可能會儲存產品的區域：
- **Freezer rooms**
- **Cold rooms**
- **Temperature-controlled storage areas**
- **Quarantine areas**
- **Receiving bays**
- **Loading bays**
- **Laboratories**

Temperature mapping of storage areas

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- 用於監測**Mapping**之設備，需具備以下條件：
- **1.** 能適用到待監測之空間範圍。
- **2.** 可持續監測溫度**-**時間之紀錄。
- **3.** 可執行合適的監測範圍**(ex： -30℃ to 60℃)** 。
- **4.** 能以週期性自動監測方式記錄。
- **(ex： 1 min to 15mins)**
- **5.** 需要有可追溯至**NIST**標準之**3**點校正報告且
- 每點校正誤差不得超出**±0.5℃**。
- **6.** 可下載數據至電腦端執行後續之結果分析。

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- 執行溫度**Mapping**研究時，至少於每個區域
- 均需考慮評量執行兩個季節變化影響，
- 一是最溫暖**(warmest season)**及
- 最冷的**(coldest season)** 。

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- 以下步驟為執行溫度**Mapping study**的重要步驟：

- **Step 1.** 選擇適當電子數據紀錄監測儀
- 一年需校正一次
- 校正誤差需小於**±0.5℃**
- 校正點：低於溫度管制範圍最低點
- 溫度管制範圍中間點
- 高於溫度管制範圍最高點

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- 以下步驟為執行溫度**Mapping study**的重要步驟：

- **Step 2.** 執行**Mapping study**成員
- 簽名樣式確認
- 工作內容職責內容說明

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- 以下步驟為執行溫度**Mapping study**的重要步驟：

- **Step 3.** 測繪待測區域
- 空間長寬高
- 劃出空間圖 包括標示各項加熱源、冷氣源、出風口及任何可能影響溫度安定性之要件
- 標示溫度紀錄儀及溫度控制**sensors**位置

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- 以下步驟為執行溫度**Mapping study**的重要步驟：
- **Step 4.** 清楚定義可接受溫度範圍值

空調系統建置與溫度異常處理要點

藥品儲存溫度範圍：

室溫：**+15** 到**+ 25 ˚C**。

低溫：**+8** 到**+ 15 ˚C**。

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冷凍：低於 **-15 ˚C**。

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以下步驟為執行溫度**Mapping study**的重要步驟：

- **Step 5.** 決定電子數據紀錄監測儀位置
- 長寬：每**5-10metres**放置一點
- 高：如樓高天花板高度為**3.6M(**或以下**)**，
- 則放置一點於接近地板處、**1.2M**處
- 以及 **3.0M**處。
- 如樓高天花板高度為**3.6M**以上，以
- **6M**高為例，則放置一點於**1.8M(30%)**
- 、**3.6M(60%)**處以及 **5.4M(90%)**處

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以下步驟為執行溫度**Mapping study**的重要步驟：

- **Step 5.** 決定電子數據紀錄監測儀位置
- 長×寬為：**14m×7m**
- 高度為：**6m**
- 需放幾個監測儀**??**

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- **Step 8.** 固定電子數據紀錄監測儀使其不易被任意移動。
- **Step 9.** 執行**7 to 10 days**連續監測。
- **Step 10. Download**監測數據。

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

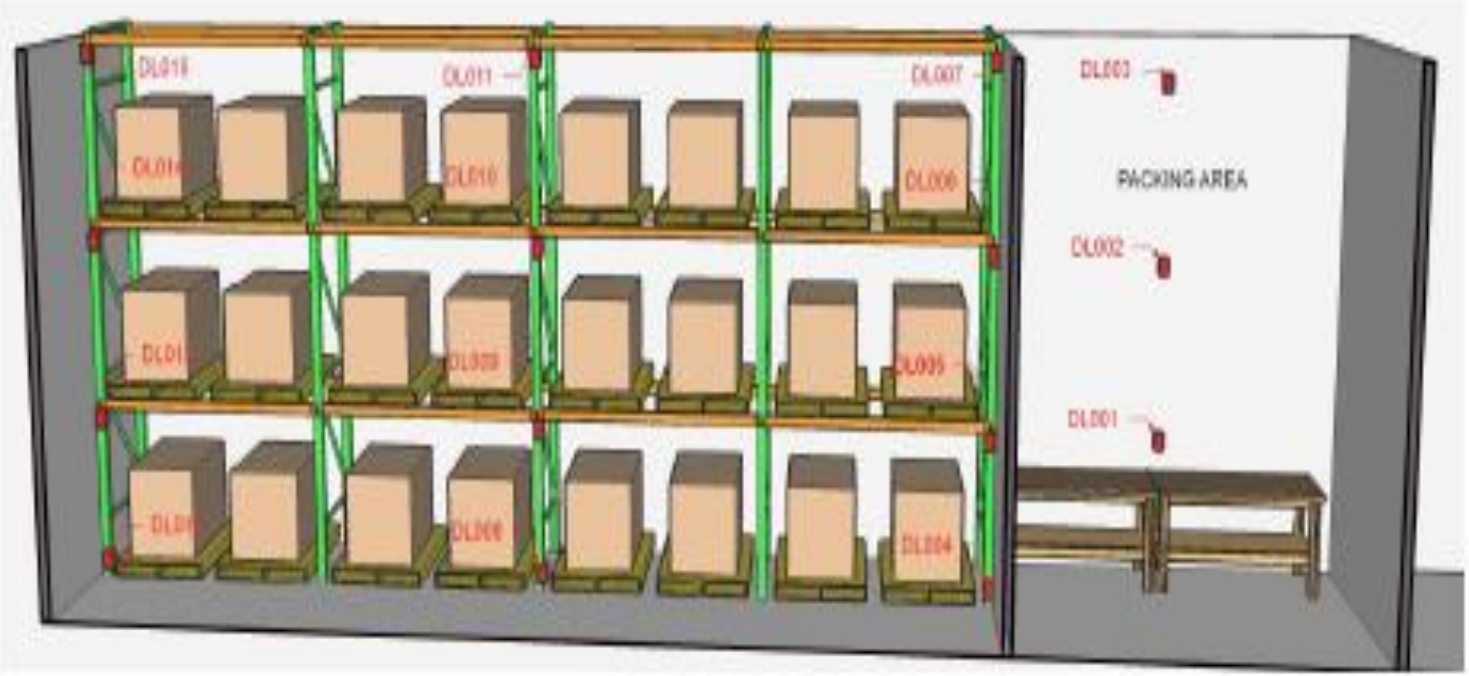

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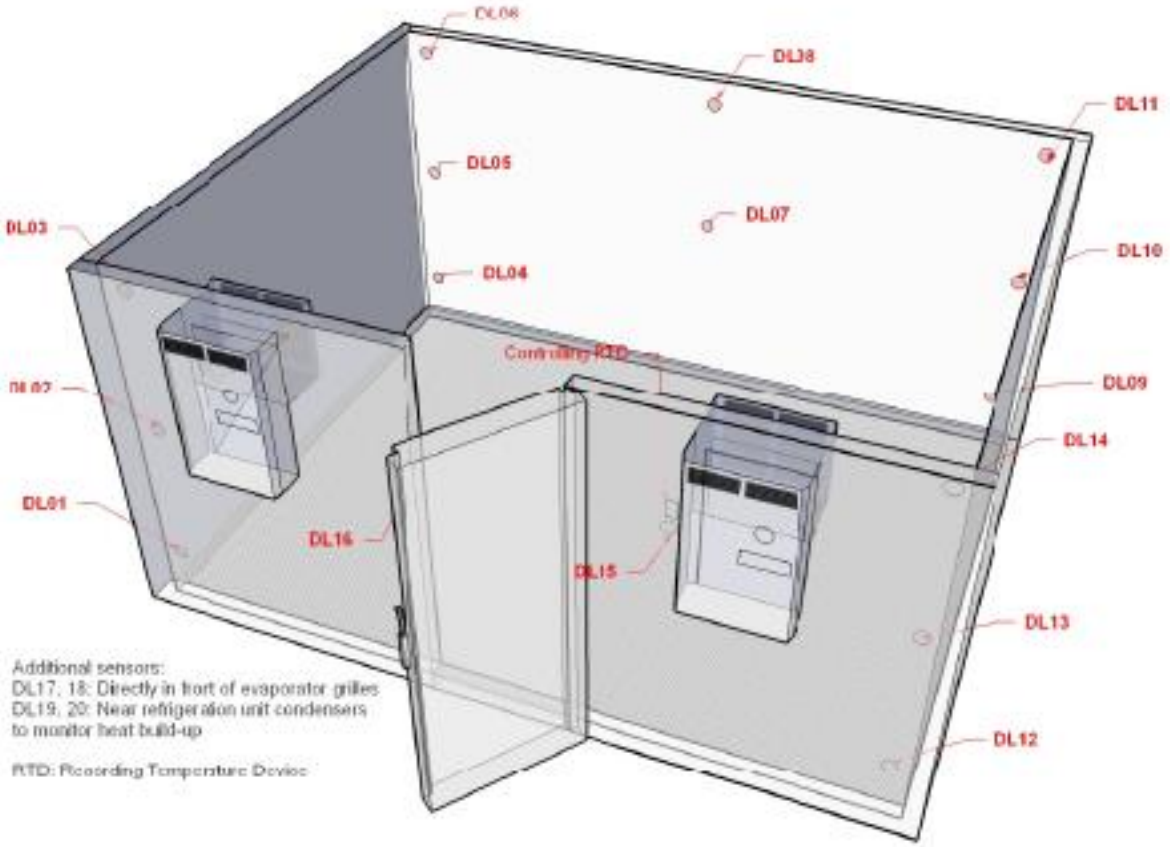
Figure 2 – Typical location of data loggers in a walk-in cold room



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- 分析監測結果：
- **(1) Minimum and maximum temperature**
- **(2) Hot and cold spots**
- **(找出日常監測位置)**
- **(3) Mean Temperatures**
- **(Mean Kinetic Temperatures (MKT))**

Temperature mapping of storage areas

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APPLICATION OF MEAN KINETIC TEMPERATURE

See *Pharmaceutical Stability* 〈 1150 〉 for the definition of mean kinetic temperature (MKT). MKT is usually higher than the arithmetic mean temperature and is derived from the Arrhenius equation. MKT addresses temperature fluctuations during the storage period of the product. The mean kinetic temperature, T_K, is calculated by the following equation:

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

in which ΔH is the heat of activation, which equals 83.144 kJ per mol (unless more accurate information is available from experimental studies); R is the universal gas constant, which equals 8.3144×10^3 kJ per degree per mol; T_1 is the average temperature, in degrees Kelvin, during the first time period, e.g., the first week; T_2 is the average temperature, in degrees Kelvin, during the second time period, e.g., second week; and T_n is the average temperature, in degrees Kelvin during the *n*th time period, e.g., *n*th week, *n* being the total number of temperatures recorded. The mean kinetic temperature is calculated from average storage temperatures recorded over a one-year period, with a minimum of twelve equally spaced average storage temperature observations being recorded (see *Pharmaceutical Stability* 〈 1150 〉. This calculation can be performed manually with a pocket calculator or electronically with computer software.

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$n = 52$

$\Delta H/R = 10{,}000$ K

$T_1, T_2, \ldots, T_n = 25\,^{\circ}C = 273.1 + 25 = 298.1$ K

$R = 0.0083144$ kJ $K^{-1}mol^{-1}$

$\Delta H = 83.144$ kJ per mol

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

$$= \frac{-10{,}000\text{K}}{ln\left(\frac{52 \times e^{-\Delta H/R \times 298.1}}{52}\right)}$$

$$= \frac{-10{,}000\text{K}}{ln\left(\frac{52 \times e^{-33.5458}}{52}\right)}$$

$$= \frac{-10{,}000\text{K}}{-33.5458} = 298.1\text{K} = 25.0^{\circ}\text{C}$$

空調系統建置與溫度異常處理要點

ECA Academy
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07.05.2014

GDP Question: When to use Mean Kinetic Temperature Calculation (MKT)?

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According to MHRA: "Mean Kinetic Temperature (MKT) should not be used to compensate for poor temperature control of storage (or transportation) facilities. It may be applied in situations where control is good but where occasional excursions may be encountered. (J. Taylor. 'Recommendations on the Control and Monitoring of Storage and Transportation Temperatures of Medicinal Products' The Pharmaceutical Journal (vol 267) July 2001).

It is not possible to obtain a meaningful MKT value from daily readings of simple max / min thermometers as temperature fluctuation is not a linear function. It is noted that some data loggers and building management systems are capable of recording multiple temperature readings over a time period and some offer the function of calculating the MKT over a given time period.

空調系統建置與溫度異常處理要點

溫度會不會異常?

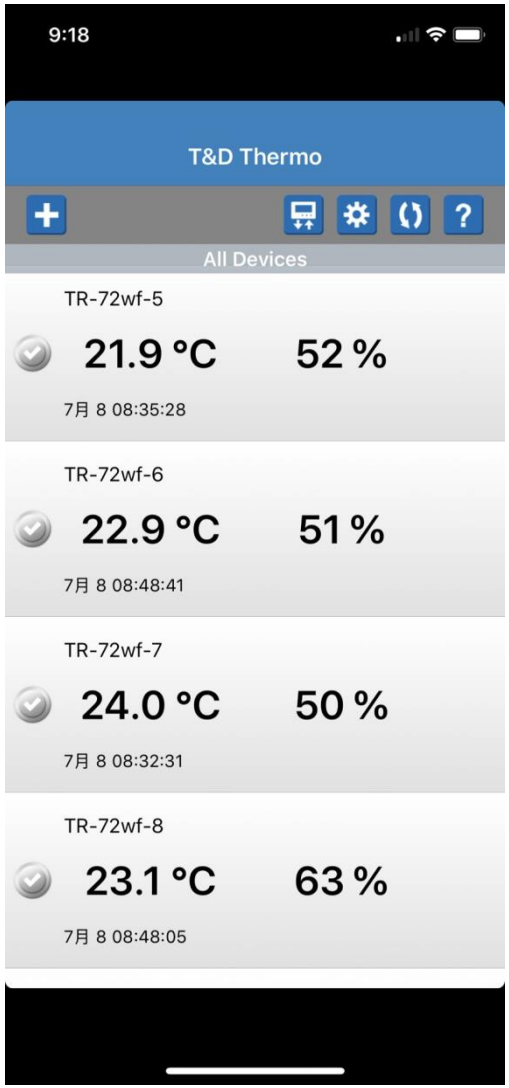
怎知溫度異常??

空調系統建置與溫度異常處理要點

3.4 設備：

3.4.3 設備之校正應可被追溯至國家或國際量測標準。設備應具備適當之警報系統以於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。

空調系統建置與溫度異常處理要點



空調系統建置與溫度異常處理要點

允許多久時間異常?

哪些資料可支持??

空調系統建置與溫度異常處理要點

USP <659> PACKAGING AND STORAGE REQUIREMENTS

Mean kinetic temperature not to exceed 25°. Excursions between 15° and 30° (59° and 86° F) that are experienced in pharmacies, hospitals, and warehouses, and during shipping are allowed. Provided the mean kinetic temperature does not exceed 25°, transient spikes up to 40° are permitted as long as they do not exceed 24 h. Spikes above 40° may be permitted only if the manufacturer so instructs.

空調系統建置與溫度異常處理要點

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.

謝謝聆聽