Annex 5

Technical supplements to Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products

(WHO Technical Report Series, No. 961, 2011), Annex 9

1. The technical supplement series

This series of technical supplements has been written to amplify the recommendations given in *Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products* (WHO Technical Report Series, No. 961, 2011, Annex 9).[1] This document sets out the principal requirements for the safe storage and distribution of time- and temperature-sensitive pharmaceutical products (TTSPPs).

The introduction to the guidance documents states that: "... supplementary materials will be developed to show how the requirements can practicably be achieved, particularly in resource constrained settings." The technical supplements, which make up this volume, are intended to provide this additional material; each one is linked back to a specific clause or clauses in the parent document. All 16 documents are written in a standard format and each contains a reference section with hyperlinks to relevant supporting materials. Most of these materials are available free online. References to print publications are minimized to avoid the difficulties associated with purchasing books and journals.

1.1 Topics covered

Table A5.1 lists the titles of the supplements and the model guidance sections to which each one refers.

Table A5.1
Titles of supplements and model guidance section to which each refers

Title	Section(s)
1. Selecting sites for storage facilities	Section 2
2. Design of storage facilities	Section 2 to 5
3. Estimating the capacity of storage facilities	Section 3.1 to 3.4
4. Security and fire protection in storage facilities	Section 3.7
5. Maintenance of storage facilities	Section 3.10
6. Temperature monitoring of storage areas	Section 4.5.2, 4.5.4
7. Qualification of temperature-controlled storage areas	Section 4.7

[1] http://www.who.int/medicines/areas/quality_safety/quality_assurance/ModelGuidanceForStorageTransportTRS961Annex9.pdf?ua=1.

Table A5.1 *continued*

Title	Section(s)
8. Temperature mapping of storage areas	Section 4.7
9. Refrigeration equipment maintenance	Section 4.9
10. Checking the accuracy of temperature control and monitoring devices	Section 4.10
11. Qualification of refrigerated road vehicles	Section 6.4, 6.5
12. Temperature-controlled transport operations by road and by air	Section 6.5, 9
13. Qualification of shipping containers	Section 6.8.1 to 6.8.4
14. Transport route profiling qualification	Section 6.8.3, 6.8.4
15. Temperature and humidity monitoring systems for transport operations	Section 6.5, 9
16. Environmental management of refrigerant gases and refrigeration equipment	Section 10.2

1.2 Target readership

The target readership for the model guidance, and for the technical supplements, includes regulators, logisticians and pharmaceutical professionals in industry, government and international agencies.

1.3 Document development and review process

The technical supplements have been written by specialist authors. All 16 supplements passed through the following editorial and public review process.

1. Each document was prepared over the course of several drafts in consultation with the series editor.
2. Acronyms and glossary definitions were harmonized throughout.
3. Public consultation drafts were posted on the WHO website in mid-2014. Review comments were received from a number of people and organizations.
4. Reviews were consolidated by the series editor and sent to the individual authors for initial comment.
5. Amended documents were prepared containing the consolidated comments categorized as "accepted", "rejected" and "for discussion".

These new drafts were sent back to the individual authors for further comment.

6. The series editor prepared final drafts based on the authors' responses and these drafts were checked, reviewed and signed off.
7. On the basis of these final comments, clean versions were prepared for review by the Expert Committee on Specifications for Pharmaceutical Preparations and by the Expert Committee on Biological Standardization.

On the following pages, the contents pages of the 16 technical supplements are reproduced. The full texts will be made available in electronic form on the CD-ROM of *Quality assurance of pharmaceuticals* (2015 and updates) and on the website.[2]

[2] http://www.who.int/medicines/areas/quality_safety/quality_assurance.

Supplement 1

Selecting sites for storage facilities

Technical supplement to

Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products (WHO Technical Report Series, No. 961, 2011), Annex 9.

Contents

Supplement 2

Design and procurement of storage facilities

Technical supplement to

Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products (WHO Technical Report Series, No. 961, 2011), Annex 9.

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Supplement 3

Estimating the capacity of storage facilities

Technical supplement to

Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products (WHO Technical Report Series, No. 961, 2011), Annex 9.

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Supplement 4

Building security and fire protection

Technical supplement to

Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products (WHO Technical Report Series, No. 961, 2011), Annex 9.

Contents

Supplement 5

Maintenance of storage facilities

Technical supplement to

Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products (WHO Technical Report Series, No. 961, 2011), Annex 9.

Contents

Supplement 6

Temperature and humidity monitoring systems for fixed storage areas

Technical supplement to

Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products (WHO Technical Report Series, No. 961, 2011), Annex 9.

Contents

Supplement 7

Qualification of temperature-controlled storage areas

Technical supplement to

Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products (WHO Technical Report Series, No. 961, 2011), Annex 9.

Contents

Supplement 8

Temperature mapping of storage areas

Technical supplement to

Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products (WHO Technical Report Series, No. 961, 2011), Annex 9.

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Supplement 9

Maintenance of refrigeration equipment

Technical supplement to

Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products (WHO Technical Report Series, No. 961, 2011), Annex 9.

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Supplement 10

Checking the accuracy of temperature control and monitoring devices

Technical supplement to

Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products (WHO Technical Report Series, No. 961, 2011), Annex 9.

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Supplement 11

Qualification of refrigerated road vehicles

Technical supplement to

Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products (WHO Technical Report Series, No. 961, 2011), Annex 9.

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Supplement 12

Temperature-controlled transport operations by road and by air

Technical supplement to

Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products (WHO Technical Report Series, No. 961, 2011), Annex 9.

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Supplement 13

Qualification of shipping containers

Technical supplement to

Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products (WHO Technical Report Series, No. 961, 2011), Annex 9.

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Supplement 14

Transport route profiling qualification

Technical supplement to

Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products (WHO Technical Report Series, No. 961, 2011), Annex 9.

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Supplement 15

Temperature and humidity monitoring systems for transport operations

Technical supplement to

Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products (WHO Technical Report Series, No. 961, 2011), Annex 9.

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Supplement 16

Environmental management of refrigeration equipment

Technical supplement to

Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products (WHO Technical Report Series, No. 961, 2011), Annex 9.

Contents

Supplement 1

Selecting sites for storage facilities

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

Annex 9: Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products

May 2015

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Abbreviations

GIS	geographical information system
TTSPP	time- and temperature-sensitive pharmaceutical product

Acknowledgements

The author of this document is Andrew Garnett, an independent consultant, London, England.

Glossary

Bunding or bund wall: A constructed retaining wall or earth embankment designed to prevent inundation or breaches from a known source.

Drainage swale: Shallow, sloped channels designed to collect and move surface run-off toward streets or holding ponds and away from buildings or houses.

Inventory turnover: A measure of the number of times inventory is sold or used in a time period such as a year. The equation for inventory turnover equals the cost of goods sold divided by the average inventory. Inventory turnover is also known as inventory turns, stockturn, stock turns, turns, and stock turnover.

Pharmaceutical product: Any product intended for human use or veterinary product intended for administration to food producing animals, presented in its finished dosage form, that is subject to control by pharmaceutical legislation in either the exporting or the importing state and includes products for which a prescription is required, products which may be sold to patients without a prescription, biologicals and vaccines. Medical devices are not included.[1]

Standard operating procedure (SOP): A set of instructions having the force of a directive, covering those features of operations that lend themselves to a definite or standardized procedure without loss of effectiveness. Standard operating policies and procedures can be effective catalysts to drive performance improvement and improve organizational results.

Time- and temperature-sensitive pharmaceutical product (TTSPP): Any pharmaceutical good or product which, when not stored or transported within predefined environmental conditions and/or within predefined time limits, is degraded to the extent that it no longer performs as originally intended.

[1] Definition from WHO/QAS/08.252 Rev 1 Sept 2009. *Proposal for revision of WHO good distribution practices for pharmaceutical products – Draft for comments*.

1. Introduction

This technical supplement has been written to amplify the recommendations given in Section 2 of WHO Technical Report Series No. 961, 2011, Annex 9: *Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products*.[2] Related topics are covered in the following supplements:

- *Estimating the capacity of storage facilities*
- *Design of storage facilities*
- *Security and fire protection in storage facilities*

1.1 Requirements

Pharmaceutical warehouse sites and other places, such as pharmacies, where significant quantities of pharmaceutical products are stored, should be located so as to minimize risks from natural hazards such as floods, landslides and earthquakes and extreme weather conditions such as hurricanes and tornadoes. In addition, sites should be located in places that enable the target population to be served efficiently by making effective use of existing transport infrastructure.

1.2 Objectives

The objective of this Technical Supplement is to provide guidance on how to meet the above requirements. This document only covers the process of choosing suitable warehouse locations; it does not cover warehouse sizing or the layout and development of the site itself – for these topics, refer to the companion Technical Supplements listed above.

1.3 Target readership

This supplement provides guidance aimed at more senior operations staff. Principally these will be the owners and operators of warehouses, pharmacies and other buildings used to store TTSPPs and those responsible for property development and property acquisition on behalf of owners and operators.

[2] http://apps.who.int/medicinedocs/documents/s18683en/s18683en.pdf

2. Guidance

The correct choice of warehouse site(s) and the associated pre-development site investigation process is a critical strategic decision for any logistics operation. The goal of supply chain system design is to minimize whole system inventory holding and distribution costs while ensuring an acceptable service level for patients and end-users. The overall efficiency of storage and distribution systems is a major driver for commercial organizations; consequently there is a large literature on this subject and much professional expertise. This supplement provides a simple introduction to some of the concepts involved and outlines some of the key decisions that need to be made.

Related topics are covered in the following supplements:

- *Design of storage facilities*
- *Estimating warehouse storage capacity*
- *Security and fire protection in storage facilities*
- *Maintenance of storage facilities*

2.1 Associated materials and equipment

Professional staff responsible for site surveys and investigations must have access to appropriate surveying and site investigation equipment.

2.2 Designing and costing the supply chain

The first step in supply chain planning is to establish the number of levels in the supply chain where storage points are required, and to determine the preferred geographical location of these stores. Traditionally, health commodities in the public sector are often stored at locations that reflect the country's administrative structure. Thus there will typically be a national-level or state-level pharmaceutical warehouse receiving products direct from manufacturers and suppliers, smaller lower level stores at provincial and district level, with hospitals and health facilities at the end of the chain. Therefore, there may be up to five storage levels before products reach the patient. This multi-level model can lead to major inefficiencies, with low inventory turnover and high inventory holding costs; it also increases the risk of product expiry during storage.

2.3 Logistics network planning

Providing the population with a reliable and uninterrupted supply of pharmaceutical products, including TTSPPs, is a nationally important strategic objective. Achieving this objective depends to a significant extent on choosing suitable storage sites that are served by secure transport routes.

Logistics operations in large commercial organizations are very cost-sensitive because their profitability and survival is entirely dependent on customer satisfaction. A great deal of effort and resources are committed to planning distribution networks and optimizing the location of storage and transhipment points using sophisticated analytical techniques. The goal is to achieve the "six rights" of logistics – the *right product* in the *right quantity* delivered to the *right place* at the *right time* in the *right condition* at the *right cost*. Health service operations can and should be motivated by a similar desire for operational efficiency and patient satisfaction. However, in the public sector, historical choices and past patterns of development will have determined the siting of the distribution network infrastructure. Thus, the scope for radical reorganization is likely to be constrained by these decisions and also by lack of resources.

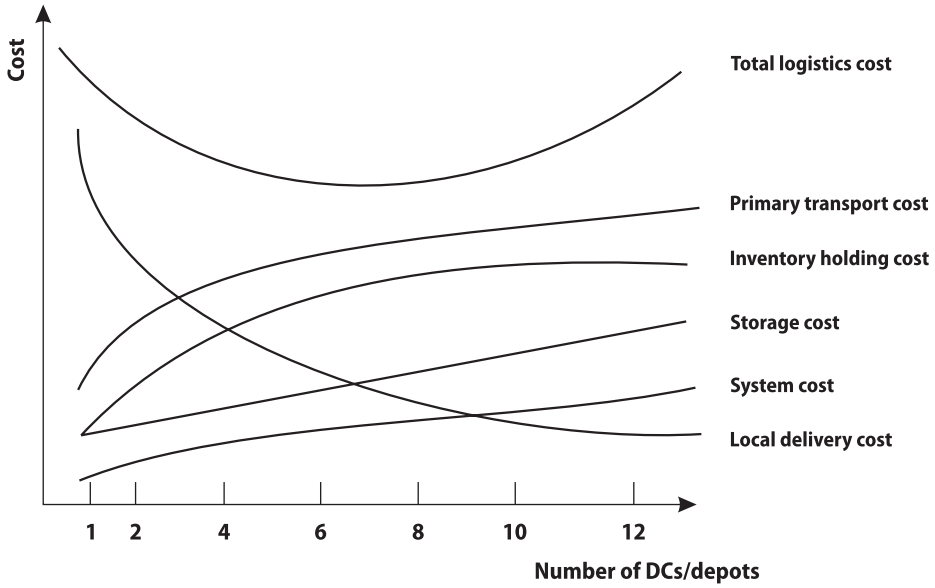
If it can be carried out, a thorough redesign of a public sector pharmaceutical distribution network should be based entirely on objective measures of cost and efficiency, rather than on preconception and historical location patterns. This is a sophisticated and specialized task. The analyst aims to achieve an optimal balance of multiple factors, including the following:

- distribution of the target population – the customers and patients;
- required service level(s) for supplied products;
- location of manufacturers and suppliers of pharmaceutical products feeding products into the distribution system;
- available transport networks (road, air, rail, water), including their condition, reliability and exposure to weather-induced delays and other hazards;
- preferred location of storage points;
- physical capacity of the storage points needed to ensure the defined level of service;
- inventory holding costs for storage facilities at the chosen locations;
- transport resources;
- transport costs.

To illustrate this approach, Figure 1 demonstrates how total logistics costs can be derived from an analysis of the individual cost elements of a logistics system – in this example a system with between one and 12 distribution centres. Here we see that the *total logistics cost* curve – the sum of the other five cost curves – shows that the lowest total system cost for this particular example is achieved with a network with six to eight distribution centres. *Primary transport* here is supply of products in full pallet loads from a central warehouse to the individual distribution centres. *Local delivery* is the distribution of product from

the distribution centre(s) to the customer. In the case of a single distribution centre, this cost element is obviously very high. *Systems cost* is the cost of operating the information systems required to manage the network.[3]

Figure 1
Total logistics costs and component cost elements



DC, distribution centre.
Source: Rushton, Croucher & Baker (2006), p. 125.

This sort of optimization exercise is not something that can be done in an ad-hoc fashion. It requires systematic strategic investigation and analysis by people who have the relevant skills, and access to the relevant data and software tools. For these reasons, detailed technical guidance is beyond the scope of the current supplement.

As an example of what can be achieved in a public sector context, the HERMES team at the Johns Hopkins Bloomberg School of Public Health has conducted extensive modelling of existing vaccine supply chains with the goal of improving their efficiency.[4] Tools have also been developed to assess supply

[3] Extracted from Chapter 8, Figure 8.7 in Rushton, Croucher & Baker (2006).

[4] http://hermes.psc.edu/

chain costs and the operational factors that drive these costs in a pre-existing context.[5] Commercial consultancies and commercial software are also widely available to handle these modelling problems.

2.4 Finding a potential site

Once a preferred general location for the warehouse has been established, the next step is to find a suitable site in the vicinity. This section addresses the main issues that need to be considered.

2.4.1 Establish the size of the warehouse

It is pointless to search for sites without first knowing the size of the building required. Clearly the design of the final building will ultimately be determined by actual site conditions; however, it is perfectly possible to make a preliminary estimate of the building footprint before any site has been acquired. An efficient warehouse layout should be as compact as possible; typically square to rectangular in plan. Awkwardly shaped sites that require non-rectangular layouts are unlikely to be a good choice.

2.4.2 Narrow down the choices

Local knowledge is the ultimate key to site acquisition. In addition, online geographical information systems (GIS) such as Google Earth™[6] and Apple Maps™[7] provide the opportunity to explore potential site locations remotely and to measure them approximately. At the same time these resources can be used to map the local transport infrastructure and connections to national networks.

The reliability of an online assessment obviously depends on how up to date the images are,[8] and on the resolution of the images themselves. Both of these factors vary around the world. Additionally, in areas undergoing rapid change it is possible that empty sites identified in this way may already have been developed.

2.4.3 Choose a secure site

Political stability and security should clearly be borne in mind, but these aspects change over time and are beyond the scope of these guidelines. However,

[5] McCord, Tien & Sarley (2013) (http://deliver.jsi.com/dlvr_content/resources/allpubs/guidelines/SuppChaiCostMeth.pdf).

[6] http://www.google.co.uk/intl/en_uk/earth/download/ge/agree.html

[7] http://www.apple.com/uk/ios/maps/

[8] For Google Earth, typically between 6 months and 3 years or more: http://www.gearthblog.com/blog/archives/2010/10/how_often_does_google_update_the_im.html

crime patterns do need to be considered because pharmaceutical warehouses contain valuable products and site protection and other security measures will be a significant factor in site development and operating costs. Consequently, bearing in mind the overarching need to serve the target population, a risk-based approach should be taken when candidate sites are evaluated with site security in mind and the following questions should be asked:

- Is the site in a high or low crime area relative to general levels of crime in the wider location?
- Will employees be able to reach the site safely?
- Will vehicles entering or leaving the site be at risk of hijacking?
- Is there a police station in the vicinity and what response time can be anticipated in the event of a crime?
- Is there a fire station in the vicinity and what response time can be anticipated in the event of a fire breaking out?
- Can the site perimeter be adequately secured?
- Can access to the site be controlled?

2.4.4 Choose a future-proof site

Wherever possible the warehouse site chosen should provide space for future expansion and should have direct access to a well-maintained free-flowing road network. Access to rail connections and nearby air or sea ports may also be necessary.

Private sector industrial and warehouse operations have similar needs, so areas of a city that are zoned for these uses are likely to be preferred locations for a pharmaceutical warehouse.

Unfortunately many cities do not have, or do not enforce, strict zoning laws. Rapid urbanization may also engulf an otherwise suitable site, radically alter accessibility, and place a severe strain on the electricity supply and other site services. These medium- to long-term risks also need to be assessed.

2.4.5 Ensure labour availability

The warehouse will require a reliable labour force, living within commuting distance. Depending upon the economic context and the availability of personal and public transport, the site evaluation needs to review the potential employee catchment area and the skills available within it.

2.4.6 Assess flood risks

It is vital for the safety and security of the products stored on site that the warehouse building should not be exposed to flood risks. In order to ensure uninterrupted deliveries and distributions it is also essential that site access will

not be affected by seasonally flooded roads. For this reason, pharmaceutical warehouses should preferably not be built on a flood plain or close to a coastline that is susceptible to inundation during storm surges. If no alternative site is available, the floor of the warehouse must be raised well above the predicted 100-year flood line, or the site must be fully protected by flood defences such as bunding or drainage swales. Such measures will inevitably increase building costs. In addition, site-specific flood defences may adversely affect neighbouring properties by locally increasing the flood risk outside the protected site.

2.4.7 Assess weather and climate-related risks

In addition to historical weather patterns, an increase in extreme weather events is a predicted effect of climate change. Pharmaceutical warehouses should be sited and constructed to minimize the consequences of these risks over the lifetime of the development – typically 30 years or more. Predictable risks include direct wind and rain damage, lightning strikes, and damage from flying debris and falling trees during high winds and tornadoes. In hilly or mountainous areas there is also a possibility of damage from rainfall-induced landslides or avalanches. The site assessment must include an evaluation of these risks and recommendations for risk mitigation. For example, a warehouse located adjacent to a shanty town area may be at greater risk of damage from flying debris than one located adjacent to well-constructed buildings.

2.4.8 Assess fire hazards

Protection of pharmaceutical warehouses against fire risks is crucial. Some risks may be a direct consequence of site location, so these risks need to be evaluated as part of the site procurement process. The first task is to establish whether there are significant hazards in the immediate vicinity – for example fire-prone bush land or fire-prone urban developments, such as nearby industrial facilities or informal settlements. The second task is to determine the location, effectiveness and likely response time of the local fire brigade and to establish whether the site has access to an adequate year-round supply of water for fire-fighting and/or operating a sprinkler-based fire suppression system[9] – see companion Technical Supplement: *Security and fire protection in storage facilities*.

2.4.9 Assess other natural hazards

Other natural hazards include earthquakes, volcanic eruptions and tidal waves. Warehouses can and should be engineered to withstand the former; volcanic

[9] Warehouses have large roof areas, so rainwater harvesting combined with on-site storage may be one way to ensure a reliable supply of water for firefighting.

eruptions and tidal waves are unpredictable and catastrophic events, which cannot be fully protected against at the level of an individual site. However, it should be possible to avoid locations that are close to known risks of this type.

2.5 Detailed site investigation: identifying risks and opportunities

Once a candidate site has been chosen for its development potential, the next step is to carry out a full site investigation. This will partly require desk-based studies and partly physical work on-site. A thorough investigation is essential as it will reveal problems that could affect the final decision to acquire the property as well as opportunities to make best use of the site.

2.5.1 Ground conditions and pollution hazards

It is prudent to dig trial holes and obtain a structural engineer's report before committing to the purchase or use of any site. Ground conditions significantly affect building costs. Building on poor ground such as landfill, shrinkable clays or expansive soils (black cotton soil) requires expensive piled foundations and/or reinforced concrete rafts. Buildings constructed on permanently frozen ground (permafrost) require highly engineered raised and ventilated floors. The cost of all these solutions is particularly high for warehouses because of their large ground floor footprint.

In mining areas there is a significant risk of settlement as a result of tunnel collapses and general ground movement. The costs associated with site remediation are high. Typically, site stabilization can only be achieved by grouting abandoned mine workings under the building with large quantities of concrete. If mining is still active, the risk of future settlement will remain, and may increase.

On brownfield sites previously used for industrial purposes there is a risk that the ground contains hazardous materials, including chemical pollutants and other toxic substances. Remediation of such sites is expensive because the affected soil must either be removed for safe disposal, or capped over.

Natural seepage of radioactive radon poses a health hazard in some geological areas because the gas can migrate through ground floor structures and accumulate inside poorly ventilated buildings. Geologically, radon is associated with uranium ores; phosphate rock; shales; igneous and metamorphic rocks such as granite, gneiss, and schist; and, occurs to a lesser degree in common rocks such as limestone.[10] The radon hazard can be managed by slab ventilation or by laying an impermeable membrane under the ground floor – again this has cost implications.

[10] http://en.wikipedia.org/wiki/Radon

Finally, ground conditions will affect the cost and effectiveness of rainwater disposal and foul water drainage. If there is no mains drainage and the ground is rocky, saturated or impermeable, septic tanks with soakaways are not effective and other solutions will have to be found.

2.5.2 Existing underground and overhead services

Sites in urban areas, especially those that have previously been developed, may well have services running across them. Buried services can include sewers, water mains, gas mains, electrical cables and telephone cables; in highly urbanized areas there may be subway lines which may prevent the use of piled foundations. In addition, there may also be overhead cables. It is essential to establish the location of such services and their ownership. Rerouting is expensive and some services may have to be retained – all of this will affect the development potential of the site.

2.5.3 Site survey

An accurate site survey needs to be carried out and a site plan drawn up; the survey should include an adequate number of spot levels to establish site contours and should also include the location of all existing buildings and identifiable above- and below-ground services and other features. This work must be completed before the design team can prepare accurate cost estimates and detailed building and site work drawings. A level survey is particularly important for a large warehouse development because significant falls across the site will affect the design of ground works and the layout of access roadways and the like. The cost of cutting and filling to create a level platform for the warehouse floor may be significant.

2.5.4 Site clearance costs

If the site has existing buildings that are to be demolished, the cost of demolition works should be assessed as part of the site investigation. Refer also to section 2.5.1 regarding potential pollution hazards arising from the demolition process and previous use of the site.

2.5.5 Building surveys

If any buildings on the site are to be retained for immediate use, or refurbished, adapted or extended, it is essential that they are included in the survey process. Each building should be physically measured and the survey team should draw up plans, sections and elevations. In addition there should be a full condition survey which includes a structural assessment by a qualified structural engineer and assessment of the mechanical and electrical services by a qualified mechanical

and electrical services engineer. Checks should be carried out to determine the presence of hazardous materials, such as asbestos.

2.5.6 Service connections to the site

A warehouse site will need adequate electricity, water supply, telephone and Internet services. In addition, if it is available, there may need to be a piped gas and sewer connection. The capacity of all these connections and services needs to be sufficient to support the proposed building(s), including any future expansion.

Information about the location and capacity of site service connections should be obtained from the relevant service authorities. At the same time it is wise to enquire about future development plans in the area because any development is likely to affect future service capacity and reliability in the medium to long term. This is especially true in urban areas experiencing rapid growth.

In the absence of suitable mains services, the site development budget will have to cover on-site provision. Power can be supplied by a diesel generator; if site conditions are favourable, water may be available from a borehole. Both will be expensive to install. Generator running costs are also likely to be high, particularly for a warehouse storing TTSPPs in cold rooms and freezer rooms, because the generator will have to run continuously. In addition, an off-grid site may well have to have duplicate generators to ensure that products are kept at the correct temperature in the event of a generator failure.

2.5.7 Low carbon energy potential

Some sites offer the potential for on-site energy generation using renewable technologies. In countries with good solar potential,[11] photovoltaic panels or solar thermal water heaters can be installed on most sites. Warehouse buildings are particularly suitable because they have large roof areas on which to mount the panels. However, it is essential to ensure that the panels are not shaded by surrounding buildings or trees. Another renewable resource that could be exploited if there is a suitable river or stream nearby is small-scale hydro power.

Rural sites with reliable wind may be suitable for wind turbines[12] and geothermal (ground-source) or air-source heat pumps can also be used as a viable source of low-carbon cooling and/or heating.[13] Both geographical location and ground conditions affect the viability of these technologies.

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[11] The WHO document: PQS solar autonomy calculation method includes a substantial database of solar radiation data (http://apps.who.int/immunization_standards/vaccine_quality/pqs_catalogue/catdocumentation.aspx?id_cat=17).

[12] It is essential that wind turbines are installed on sites where there are no nearby buildings or trees; as a general rule they do not operate effectively in urban areas.

[13] http://en.wikipedia.org/wiki/Geothermal_heat_pump

2.5.8 Environmental impact assessment

If the site is located in an area of high biodiversity, careful consideration should be given to the impact of the development on habitat loss. Sensitive development and careful landscaping treatments can limit damage, but will not prevent it. It is important to note that abandoned urban land (brownfield sites) often have high levels of biodiversity; especially of plants and invertebrates. Small-scale habitats such as these are relatively easy and inexpensive to maintain and protect.

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Revision history

Date	Change summary	Reason for change	Approved

Supplement 2

Design and procurement of storage facilities

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

Annex 9: Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products

May 2015

Contents

Abbreviations

BREEAM	building research establishment environmental assessment method
CCTV	closed-circuit television
EEFO	earliest-expiry-first-out
FIFO	first-in-first-out
IFRC	International Federation of Red Cross and Red Crescent Societies
ISO	International Standards Organization
LEED	Leadership in Energy and Environmental Design
MSF	Médecins Sans Frontières
PPP	public–private partnership
SIA	supplementary immunization activity
SKU	stock-keeping unit
TTSPP	time- and temperature-sensitive pharmaceutical product
UPC	Universal Product Code
VEN	vital, essential, nonessential

Acknowledgements

The author of this document is Andrew Garnett, an independent consultant, London, England.

Glossary

ABC analysis: Tool for reviewing stock movement, which categorizes items by the volume and value of consumption during a specific period of time, usually one year. Class A items – 10–20% of items, representing 75–80% of expenditures – are mostly high-volume, fast-moving medicines. Class B items are usually 10–20% of items, and 15–20% of expenditures. Class C items often represent 60–80% of the items but only about 5–10% of the total expenditures; these are the low-volume, slow-moving items. Thus, class C is a good place to look for items that might not be needed in stock at all times. See also *VEN analysis*.

Client: The organization or individual that is responsible for procuring a building development; sometimes referred to as the *employer*.

Controlled or hazardous products: TTSPPs and other products with high illicit value: poisons, narcotics, psychotropic products, inflammable or explosive substances and radioactive materials.

Insulated shipper: A single-use insulated passive container, containing coolant, typically used to distribute TTSPPs by road or air transport.

Inventory turnover: A measure of the number of times inventory is sold or used in a time period such as a year. The equation for inventory turnover equals the cost of goods sold divided by the average inventory. Inventory turnover is also known as inventory turns, stockturn, stock turns, turns, and stock turnover.

Net storage capacity: The total volume available for storing TTSPPs, taking account of the type of load support system employed (floor-standing pallets, adjustable pallet racking, shelving units or cabinet). Net storage capacity is calculated by multiplying the gross storage capacity of the load support system by the utilization factor (less than one) that can be achieved for the chosen stock-keeping unit type.

Pallet: Wooden or plastic platform designed to be lifted by pallet jack or forklift truck. Typically used for storing and handling tertiary cartons.

Passive systems: Systems which maintain a temperature-controlled environment inside an insulated enclosure, with or without thermostatic regulation, using a finite amount of preconditioned coolant in the form of chilled or frozen gel packs, phase change materials, dry ice or others.

Pharmaceutical product: Any product intended for human use or veterinary product intended for administration to food producing animals, presented in its finished dosage form, that is subject to control by pharmaceutical legislation in either the exporting or the importing state and includes products for which

a prescription is required, products which may be sold to patients without a prescription, biologicals and vaccines. Medical devices are not included.[1]

Primary container: Bag, blister pack, strip, bottle, cartridge, vial, ampoule, prefilled device, plastic dispenser, tube, single dose container or the like containing tablet(s), capsule(s), liquid preparation or the like.

Refrigeration equipment: The term "refrigeration" or "refrigeration equipment" means any equipment whose purpose is to lower air and product temperatures and/or to control relative humidity.

Secondary pack or carton or market package: The package presentation intended for the end-user (e.g. bottle + cap liner + dose cap + leaflets + carton) but not including packaging used solely for transport purposes (e.g. *Tertiary carton or Insulated shipper*). The secondary pack may contain multiple units of product.

Staging area: Zone(s) of a warehouse designated for the short-term storage of incoming goods waiting to be moved into long-term storage, and also for storing outgoing goods awaiting shipment.

Standard operating procedure (SOP): A set of instructions having the force of a directive, covering those features of operations that lend themselves to a definite or standardized procedure without loss of effectiveness. Standard operating policies and procedures can be effective catalysts to drive performance improvement and improve organizational results.

Stock-keeping unit (SKU): In the field of inventory management, a code number, typically used as a machine-readable bar code, assigned to a single item of inventory. As part of a system for inventory control, the SKU represents the smallest unit of a product that can be sold from inventory, purchased, or added to inventory. Applied to wholesale, retail, or production operations, the SKU can assist in monitoring transactions, tracking customer spending patterns, controlling inventory and purchasing, and providing information about pricing,[2] for example via its Universal Product Code (UPC). In the context of this Technical Supplement, and depending on the level in the supply chain, an SKU may be a complete pallet, a tertiary carton, a secondary carton or a primary container.

Temperature-controlled: Includes any environment in which the temperature is actively or passively controlled at a level different from that of the surrounding environment within precise predefined limits.

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[1] Definition from WHO/QAS/08.252 Rev 1 Sept 2009. *Proposal for revision of WHO good distribution practices for pharmaceutical products – Draft for comments*.

[2] Source: http://www.britannica.com/EBchecked/topic/1242199/SKU

Temperature-modified: Includes any environment in which the temperature is predictably maintained at a level different from that of the surrounding environment, but is not actively or passively controlled within precise predefined limits.

Tertiary pack or carton: The pack or carton that contains a number of secondary cartons; usually constructed of corrugated fibreboard. *Note*: the tertiary carton is not the same as the insulated shipper used for international air shipment of TTSPPs, although the insulated shipper may contain one or more of these cartons.

Time and temperature-sensitive pharmaceutical product (TTSPP): Any pharmaceutical good or product which, when not stored or transported within predefined environmental conditions and/or within predefined time limits, is degraded to the extent that it no longer performs as originally intended.

Utilization factor: The percentage of the total volume available for storing TTSPPs that can reliably be achieved in practice, taking account of the types of stock-keeping unit, the types of load support system and the stock management systems used in the store.

VEN analysis: Method for categorizing stock as vital (V), essential (E), or nonessential (N). This system is sometimes modified to two categories – V and N. VEN analysis is often used to prioritize procurement when not enough funds exist to purchase all items requested. The system can also help determine which items should be kept in stock and which can be ordered when needed. See also *ABC analysis*.

1. Introduction

This technical supplement has been written to amplify the recommendations given in Sections 2 to 5 of WHO Technical Report Series No. 961, 2011, Annex 9: *Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products*.[3] Related topics are covered in the following technical supplements:

- *Estimating the capacity of storage facilities*
- *Maintenance of refrigeration equipment*
- *Maintenance of storage facilities*
- *Qualification of temperature-controlled storage areas*
- *Security and fire protection in storage facilities*
- *Selecting sites for storage facilities*
- *Temperature-controlled transport operations*
- *Temperature and humidity monitoring systems for fixed storage areas*
- *Temperature mapping of storage areas*

1.1 Requirements

Pharmaceutical warehouses need to be efficiently laid out and should contain all the necessary storage areas, goods assembly, packing, receiving and dispatch bays and office and ancillary accommodation needed for the effective operation of the store. Pharmacies and health facilities should be laid out so as to minimize dispensing errors and should provide a safe and comfortable environment for staff and patients. Facilities of all sizes and types must be able to store and protect TTSPPs and other products against damage and degradation during storage.

1.2 Objectives

This document provides general advice on the process of designing, procuring and commissioning pharmaceutical warehouse buildings which are intended to store pharmaceutical products, predominantly under temperature-controlled conditions. It also touches on issues relating to the design of smaller scale facilities, such as pharmacies. It covers the following topics:

- the main design requirements for a pharmaceutical warehouse or dispensing facility
- preparing and agreeing a design brief

[3] http://apps.who.int/medicinedocs/documents/s18683en/s18683en.pdf

- appointing and working with a design team
- choosing a procurement route
- the client's role in tendering
- the client's role during the construction stage
- commissioning and handover

The overall objective is to help the reader to act as an informed client. This supplement contains general guidance material only. It assumes that a professional design team will be commissioned to work with the client to determine the required capacity of the facility, develop a detailed site-specific building brief, prepare outline drawings for client approval, prepare construction and tender documentation, and be responsible for overseeing the construction and commissioning process. Alternatively, most of these essential tasks may be carried out as part of a turnkey offer from a suitably qualified construction company.

Although it provides links to some useful online resources, the supplement is not intended to be a detailed design guide. Readers are advised to consult the reference documents in order to obtain a fuller understanding of this extensive subject.

Note: Before any storage facility can be designed, it is essential to identify and quantify the products to be stored in the facility and to establish the specific environmental and security conditions under which each of these products must be kept. Readers should refer to the companion supplement: *Estimating the capacity of storage facilities*.

1.3 Target readership

This supplement will be of use to senior personnel responsible for procuring public sector medical warehouses and other related facilities. Such a person will generally be responsible for the entire procurement process, will act as the client and will be responsible for preparing the building brief, appointing and managing the design team and overseeing the construction and commissioning process.

2. Guidance

Well designed, correctly sized, suitably located and well managed pharmaceutical stores, pharmacies and other facilities, combined with an efficient distribution system, can significantly improve the operational efficiency of a health service by ensuring that patients receive the correct medicines in good condition and in a timely fashion.

2.1 Associated materials and equipment

None required.

2.2 Design of pharmaceutical warehouses

Comprehensive guidance on the design, layout and operation of medical warehouses is given in the online document, *Guidelines for warehousing health commodities*, published by JSI | DELIVER. The guidelines include an overview of warehouse planning and cover the various types of load support system, including shelving, pallet racking, gravity flow systems and carousels, and the selection and the use of materials handling equipment such as pallet jacks and forklift trucks. It also provides guidance on human resource planning, warehouse management systems and the use of bar coding technology. Another comprehensive reference, which includes case studies, is the online guide from Link51: *Racking & warehouse storage guide*. Other useful sources of design advice are given in the References.

This section starts with a general overview of warehouse layout planning and then concentrates on design issues that relate specifically to temperature-controlled storage. These topics are not specifically covered in the JSI guidelines.

2.2.1 Low-carbon design and environmental auditing

A recognized and appropriate environmental audit system, such as the Building Research Establishment Environmental Assessment Method (BREEAM), Leadership in Energy and Environmental Design (LEED) or Pearl, should be adopted at the beginning of the design stage. All three audit schemes can be used to guide and evaluate the design and to assess the subsequent operational performance of the completed building.[4]

Temperature-controlled warehouses are potentially energy-intensive because they incorporate energy-hungry refrigeration and ventilation systems.

[4] The BREEAM, LEED and Pearl audits are internationally recognized. The Pearl rating system has been developed by the Abu Dhabi Urban Planning Council to suit the needs of desert climates. Each of the three systems has a different emphasis – for example the Pearl system has a particular focus on water conservation.

However, careful design can greatly reduce energy consumption and it is possible to design these buildings so that they are *net-zero energy*; in other words, they generate as much energy as they consume from an ambient energy source such as passive heating and cooling, roof-mounted photovoltaic panels or other renewable energy sources. Useful guidance material has been published which describes the various measures that can be taken to minimize warehouse energy consumption in a range of climate zones.[5,6] In addition, careful choice of locally available construction materials can further reduce the whole-life environmental impact of the project.

2.2.2 Warehouse layouts

Warehouse layout is dictated by the type of warehousing operation and the need to achieve an efficient flow of goods into and out of the building; it is also constrained by the physical layout of the site and available road access points. In addition, it will need to allow for future expansion and to take into account that the internal layout is certain to be changed over the life of the building, both to accommodate new product lines and to implement new warehouse technologies. Designing the building for long-term flexibility is therefore critical.

Type of operation

The focus of this supplement is the *transhipment warehouse*, a type that receives products in bulk from multiple suppliers, stores them for a period of time and then breaks them down into suitably sized stock-keeping units (SKUs) for onward delivery to lower level stores or health facilities. Depending upon the extent of bulk breaking at the higher level – say from a pallet SKU to a tertiary carton SKU – lower level stores may also have a break-bulk function; for example from the tertiary carton down to the secondary carton.

An alternative delivery approach, which largely eliminates the lower level storage function, is the *cross-dock centre*. This serves as a local hub for a radial distribution arrangement. Products are received in bulk from a transhipment centre, but with individual packages already labelled and sorted by end destination – for example a pharmacy or health facility. The packages are not put away into stock but are sent out on local delivery vehicles. Items remain in the warehouse for the shortest time possible, with same-day dispatch as the target.

Layout options

There are two main layout options – the "U" flow or the "through" flow. Figure 1 shows the "U" flow arrangement.

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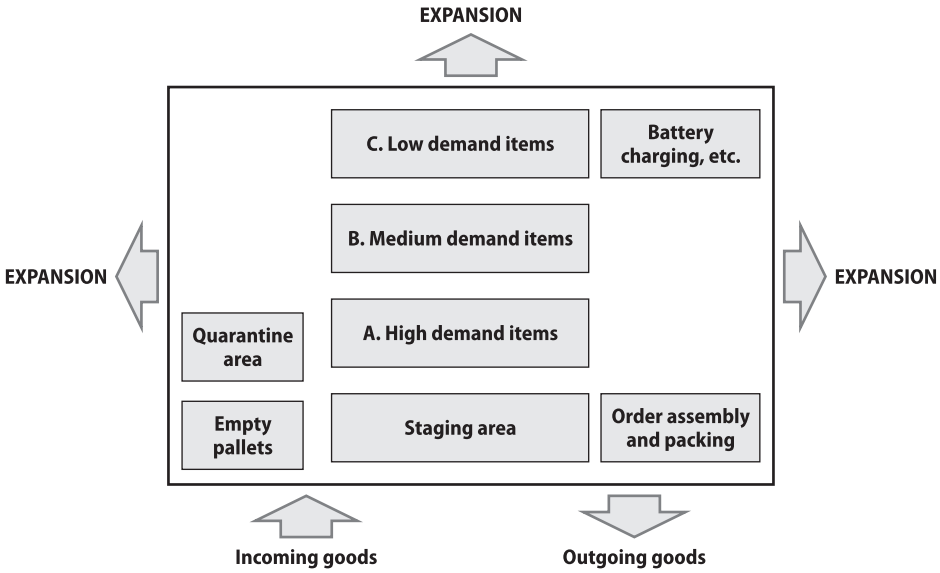
[5] American Society of Heating, Refrigerating and Air-Conditioning Engineers (ASHRAE) (2008).

[6] Target Zero. *Guidance on the design and construction of sustainable, low carbon warehouse buildings*.

Figure 1
"U" flow warehouse



Source: Adapted from Richards (2011).

The areas for goods receipt and dispatch are located on the same side of the building and products are taken into stock in accordance with their ABC designation, with the highest demand items nearest the loading bays.

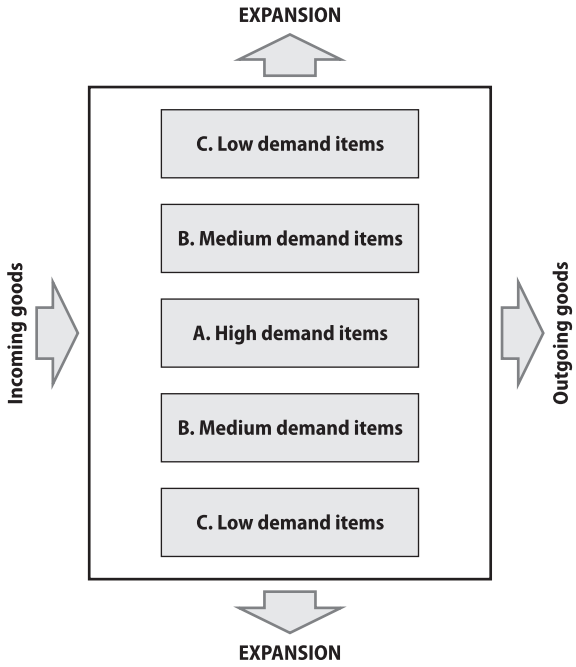
Advantages of "U" flow include:

- good utilization of dock resources because the receiving and shipping processes can share dock doors;
- facilitation of cross-docking because the receiving and dispatch areas are next to one another and can operate together;
- excellent lift truck utilization because put away and retrieval trips are easily combined and storage locations closest to the receiving and dispatch docks are natural locations to house fast-moving "A"-rated items;
- excellent security provision, because only one side of the building is used for entry and exit;
- scope for expansion in three directions.

A disadvantage of the "U" flow arrangement is that congestion can occur if there is heavy incoming and outgoing traffic at the same time.

Figure 2 shows the "through" flow arrangement.

Figure 2
"Through" flow warehouse



Source: Adapted from Richards (2011).

In a "through" flow warehouse, the areas for goods receipt and dispatch are located on opposite sides of the building. High demand items are stored along the central axis. The advantage of this arrangement is that there is little risk of congestion at the loading docks. However, security is more of a problem because of the two-sided arrangement. This is likely to require two security gates with access roads on both sides of the building. In addition, the potential for expansion is limited to two directions.

Temperature zones

The size and layout of the temperature zones within the warehouse will be determined by the labelled storage temperatures of the products to be stored, the volume of goods in each category and the SKU for each product type. See Technical Supplement: *Estimating the capacity of storage facilities*. In addition, ABC or VEN analysis (assessing whether products are vital (V), essential (E), or nonessential (N)) will determine how accessible the product needs to be, and how it will be picked during order assembly. See: JSI | DELIVER: *Guidelines for warehousing health commodities*.

2.2.3 Temperature-controlled storage areas

In this context, a temperature-controlled storage area is a zone in which the temperature is consistently maintained within a predefined temperature range, but above that required for refrigerated or frozen storage; a typical range is +15 °C to +25 °C. In this type of store, temperature is most efficiently controlled by a balanced combination of active and passive techniques. Depending on the climate, these are likely to include:

- an external building envelope with a high standard of thermal insulation;
- tight control of air infiltration through the external envelope;
- control of heat loss and heat gain during door openings; this can be achieved using lobbies and strip curtains;
- passive or low-energy heating and cooling systems such as ground-source heat pumps, night-time cooling[7] or evaporative cooling;
- control of temperature stratification using a purpose designed de-stratification system that maintains even temperature distribution throughout the volume of the temperature-controlled zone.[8]

Uncontrolled temperature stratification is a major problem in a pharmaceutical warehouse. Even in temperate climates, summer temperatures in excess of 35 °C can occur in high-bay warehouses if de-stratification measures are not taken; temperatures as high as this expose pharmaceutical products and medical devices to the risk of heat-damage.

In some settings, relative humidity will also need to be actively controlled, especially in humid climates where the dew point may well lie within the controlled temperature range.[9] Under these circumstances, high humidity and condensation may affect the stored product.[10]

2.2.4 Cold rooms and freezer rooms

The design requirements for cold rooms and freezer rooms are similar to those described for temperature-controlled stores. Products labelled for storage in the sub-zero and +2.0 °C to +8.0 °C ranges represent a small percentage of all

[7] Night-time cooling uses cool air purging to replace air that has warmed up during the day. Alternatively, cool air can be circulated through structural voids to cool the structure itself.

[8] See for example: *Pharmaceutical warehouse temperature control* http://jetenvironmental.com/pharmacetical-warehouse-temperature-control

[9] In one West African country, the dew point can be as high as +23 °C.

[10] See: US Food and Drug Administration (FDA) (2003).

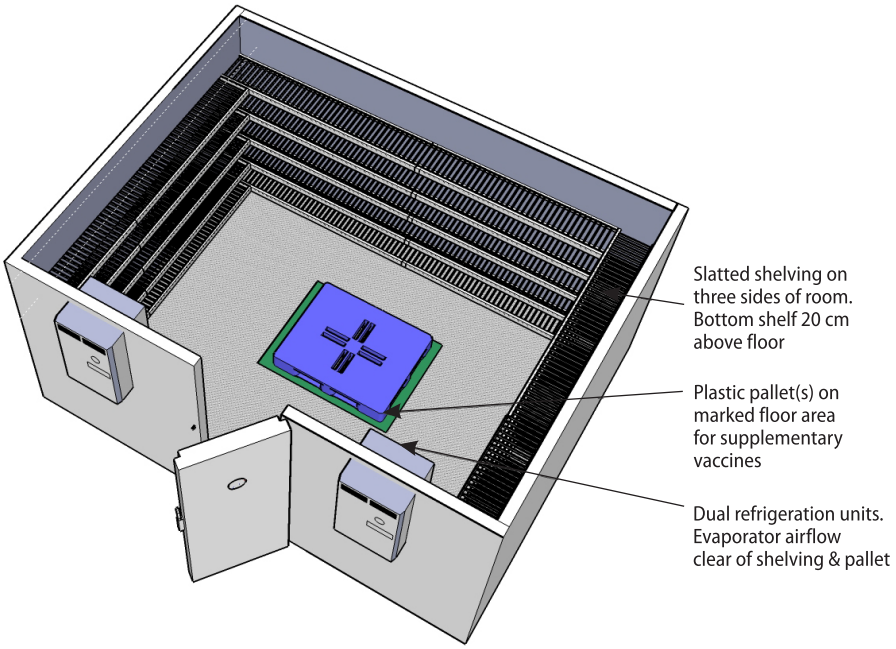
pharmaceuticals. Consequently, in a warehouse storing general pharmaceuticals, cold rooms and freezer rooms will only occupy part of the building.

Typically cold rooms and freezer rooms will be constructed within the main building envelope, using prefabricated insulated panels. All rooms should have 100% standby capacity in the event of a refrigeration unit failure. It is important for maintenance and inspection purposes to locate the room enclosure so that both wall panels and roof panels can be accessed – see companion Technical Supplement: *Maintenance of refrigeration equipment*.

Depending on the product volumes involved and the available ceiling height in the warehouse building, there are three approaches to laying out the rooms.

Walk-in rooms with shelving: For smaller rooms up to 100 m³ or so the simplest arrangement is to build walk-in rooms with adjustable shelving as the load support system. Figure 3 illustrates a typical arrangement. This particular arrangement includes an area in the centre of the room for the temporary storage of campaign vaccines and other overspill products.

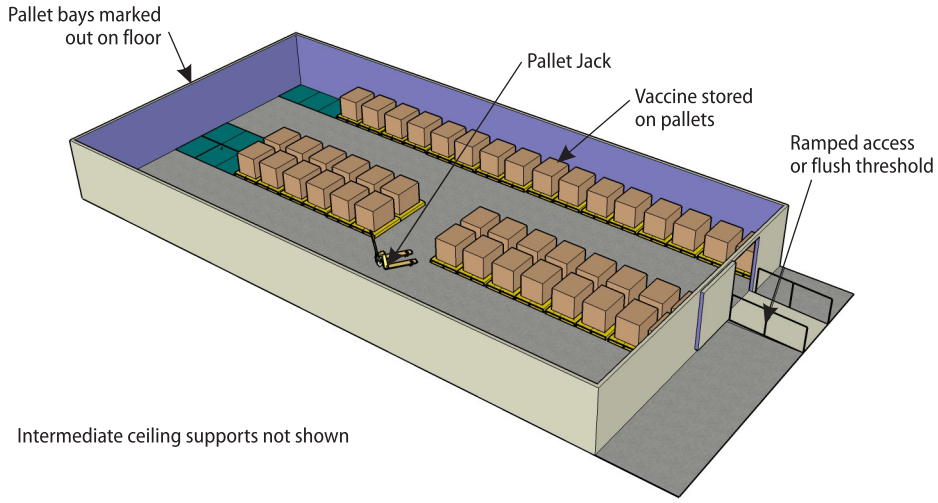
Figure 3
Walk-in cold room



The diagram shows dual "monobloc" refrigeration units. Monobloc units are easy to install but discharge waste heat from the condenser into the general warehouse space. Particularly in hot climates, a better arrangement is a "split" system with the condenser unit located outside the building.

Walk-in units generally have a floor constructed of insulated panels. These are strong enough to take foot traffic or light trolleys but they are not suitable for heavy mechanical handling equipment. In the case of a freezer room, it is generally necessary to install a heater mat below or within the floor panels. This prevents sub-zero temperatures propagating through the main floor of the building and freezing the subsoil. Over time, subsoil freezing will cause frost-heave which can crack a concrete slab.

Figure 4
Pallet standing store

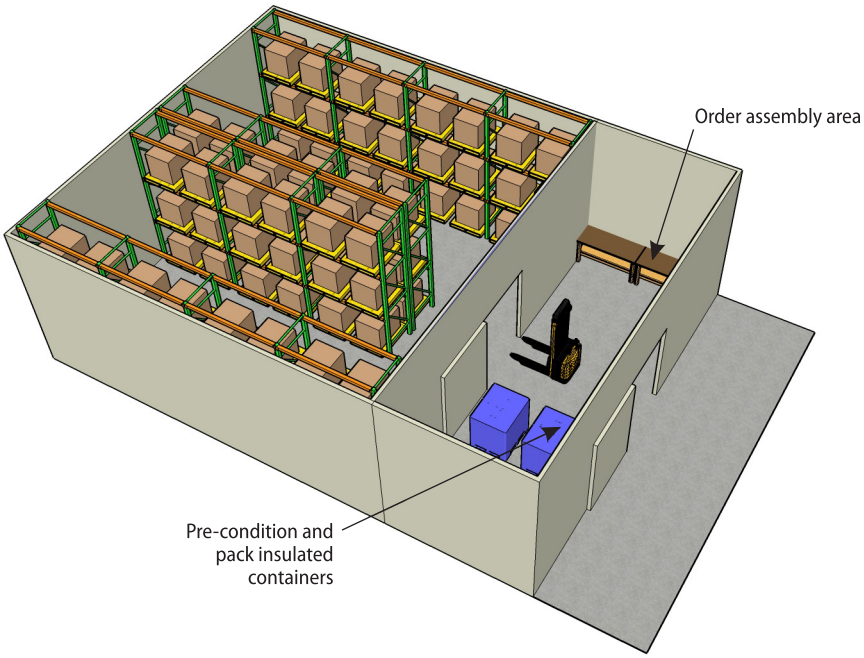


Pallet standing: This arrangement can be used for larger cold rooms where the product is stored on pallets and there is insufficient height to install pallet racking. Figure 4 shows a typical layout. Here, the pallets are moved using manual pallet jacks or electric low-lift trucks. The refrigeration units should be split systems, arranged so as to ensure a constant even temperature distribution throughout the room. The insulated floor in a pallet-standing store needs to have sufficient load capacity to support the specified mechanical handling equipment. Typically the floor will be concrete, with an insulation layer below the slab. The floor should be clearly marked to show permitted pallet positions. These positions should take account of the type of mechanical handling equipment used in the

store, the need to ensure even air distribution and any restrictions on location determined during temperature mapping of the room.[11]

The refrigeration units and floor construction are similar to those described for a pallet standing store. Load handling will require a counterbalanced electric lift truck. Depending on the size of the room and the planned level of stock movement, this may be pedestrian-controlled, or a stand-on or sit-on model.

Figure 5
Pallet racking cold room with temperature-controlled packing area



2.2.5 Order assembly and packing area

All products should be packed at or close to their labelled temperature. Depending on the type of products being handled and the way they are packed, the order assembly and packing area may be separated from the staging area, or be part of it. If most of the products are kept in the temperature-controlled zone, it may be necessary to have a separate order assembly and packing area for TTSPPs labelled at +2.0 °C to +8.0 °C or below. One possible option is to do this in an area immediately adjacent to the cold room where the product is stored – see Figure 5.

[11] See companion technical supplement: *Temperature mapping of storage areas*.

If passive containers are used for these products, the packed containers may then be moved to the general staging area, although this may reduce the cold life of the container if the holding period is very long.

If refrigerated trucks are used and TTSPPs are packed in uninsulated containers, the holding area must be contiguous with the loading dock and kept at, or close to, the labelled temperature of the product until the truck is loaded.

2.2.6 Staging area

The staging area is situated next to the loading dock. This is the zone where incoming and outgoing goods are held for dispatch or temporarily stored in preparation for putting away into stock, or for moving returned or counterfeit products into quarantine. The temperature of the staging area should reflect the type of goods held and the way in which these goods are packed.

If TTSPPs are being shipped in passive systems it is prudent to control the temperature in the staging area; this limits the exposure of the package to excessively high or low temperatures and extends its cold life while it is waiting to be transferred to storage, or to be loaded onto a vehicle. See Technical Supplement: *Temperature-controlled transport operations*.

If TTSPPs are being shipped in uninsulated packages, by refrigerated vehicle, the staging area must be fully within the temperature-controlled zone. This is essential in order to minimize exposure of the product to temperatures above or below their labelled storage range while awaiting transfer.

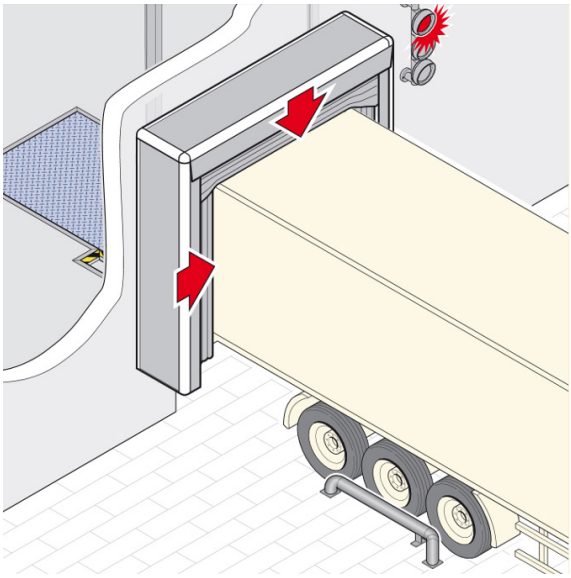
2.2.7 Loading docks

The loading dock floor may be at ground level, it may be raised to the height of a standard delivery vehicle, or there may be a height-adjustable mechanism to accommodate vehicles of different sizes. The choice will depend on the size of the operation and the types of vehicle entering and leaving the site.

In order to minimize heat loss or heat gain through the dock area, vehicles should preferably be coupled to the building by a dock seal; it must also be possible to close off the opening when no vehicle is in place. This arrangement is essential where vehicles are coupled to a temperature-controlled loading bay or holding area. Figure 6 shows an example of an insulated, inflatable dock seal suitable for this application. Extended dock seals are also available, incorporating a dock levelling platform.

If there is a mixture of large and small vehicles – for example refrigerated trucks delivering bulk products on pallets to the receiving bay and outgoing delivery vans collecting small consignments of picked products at the dispatch bay – it is likely that a combination of raised and level docks will be needed.

Figure 6
Dock seal



Source: http://www.hormann.co.uk

2.2.8 Other areas

A designated and locked area is necessary for holding counterfeit and returned products. There may also be a requirement for a sampling area and secure zones for keeping dangerous goods and controlled drugs, some of which may be TTSPPs. If explosive substances are stored, these should be in a separate explosion-proof area fitted with an explosion hatch. The hatch should be arranged so that there is no risk to staff or passers-by in the event of an accident.

2.2.9 Temperature monitoring, mapping and qualification

All freezer rooms, cold rooms and temperature-controlled storage, packing and staging areas must be equipped with continuous temperature and/or humidity monitoring equipment as described in the companion supplement: Temperature and humidity monitoring systems for fixed storage areas.

In addition, all these areas should be qualified and temperature-mapped – see companion supplements: *Qualification of temperature-controlled storage areas* and *Temperature mapping of storage areas*. Initial mapping should be carried out in both the hot and cold seasons. Mapping should be repeated at regular intervals and after any significant modification to the building, the stock layout, or the heating or cooling system.

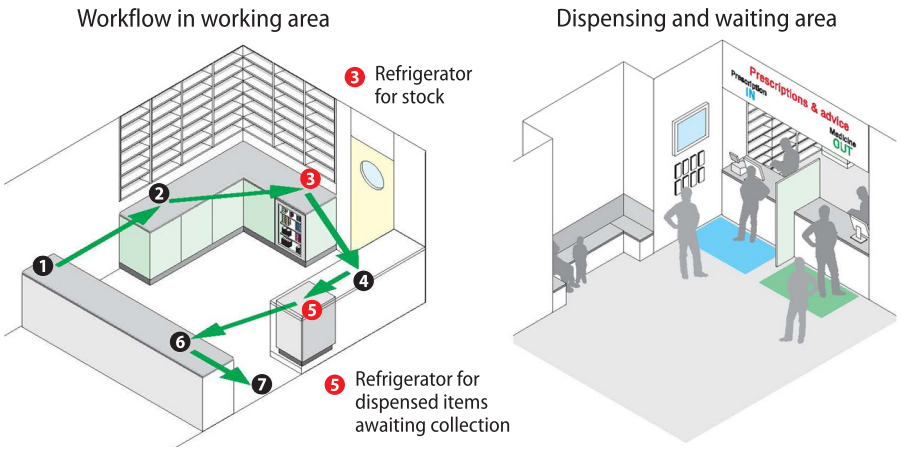
2.3 Design of dispensing facilities

Dispensing facilities range in size from large hospital and private sector pharmacies down to small-scale rural health facilities. In many types of facility, the area devoted to storage will occupy a small part of the building footprint – in the smallest facilities it may simply be a medicine cupboard and a refrigerator. However small the facility, due regard should be given to the basic principles of temperature and humidity control and the physical security of the products being stored – effectively the same requirements that apply in a pharmaceutical warehouse.

As well as storing pharmaceuticals and related supplies, dispensing facility operations also involve direct or indirect contact with the patient. There are three main types of contact: issue of medicine for self-administration at home, issue for supervised consumption at the dispensing point, or issue for use during a medical intervention by a health worker.

In addition to the risks associated with incorrect storage practices, which are common to all storage operations, there is the added risk of dispensing error, or errors arising from miscommunication with the patient or health worker. These risks can be mitigated by good ergonomic design, effective organization of stored products, and efficient workflow. A comprehensive online design guide, published by the UK National Health Service, addresses these issues.[12] Figure 7 illustrates the layout of the working area and one arrangement for the dispensing area.

Figure 7
Pharmacy layout



Source: http://www.hormann.co.uk

[12] See: National Health Service (NHS) National Patient Safety Agency (2007).

The following subsections highlight some of its key recommendations, specifically those that relate to the physical layout of a dispensing pharmacy.

2.3.1 Workflow

Effective workflow planning is as critical in the dispensing environment as it is in a warehouse. Dispensing is a multi-stage process and it is important to identify and understand the importance of each step. Poorly-planned workflow can result in confusion, fatigue and increased risk of error.

- The pharmacy layout should promote efficient workflow; this positively affects dispensing activity, allowing pharmacists more time for patient counselling.
- Break the workflow process down into its constituent parts, look at each individual stage, and take steps to make each stage as safe as possible.

2.3.2 Working environment and ergonomics

A good working environment promotes safe working and reduces stress levels for both staff and patients.

- Provide good quality lighting, especially over dispensing benches and near computer screens. Evidence shows that high levels of illumination with daylight-type luminaires significantly reduce dispensing errors.
- Keep the working environment at a comfortable temperature, below +25 °C, and at a comfortable humidity level.
- Ensure that work surfaces, shelving and computer workstations are designed to minimize fatigue.
- Use grey or cream coloured finishes on dispensing benches. White surfaces provide an unsuitable background for viewing white packaging and medication.
- Minimize background noise by screening and other design approaches.
- Take appropriate measures at the dispensing point to make sure that both staff and patients feel secure.
- Cushioned flooring alleviates tiredness and helps staff stay alert.

2.3.3 Incoming stock

If newly delivered stock is mixed with current stock before it is checked off, there is a risk that it will be put away in the wrong storage area.

- Assign a temporary area for storage of delivered stock before it is put away.
- Have a dedicated bench section for unpacking and checking off.
- Ensure that TTSPPs can be unpacked, checked off and immediately put away into the designated refrigerator.

2.3.4 Refrigerators

Cluttered and overstocked refrigerators make it difficult to select the correct medicine. If stock and completed prescriptions are kept in the same refrigerator, the two may get mixed up.

- Have one refrigerator for stock and another for completed prescriptions, with the latter located near the prescription collection point. If a single refrigerator has to be used, find an effective way of separating dispensed medicines from stock so that they cannot be confused with one another.
- Arrange the stock so that it is well spaced and easily seen.
- Use refrigerators that are suitable for the operating environment.[13] Glass-fronted pharmacy refrigerators allow stock to be checked without opening the door. However, this type of equipment is not suitable in places with unreliable electricity supplies because the holdover time during a power cut is too short.
- Provide refrigerators with continuous temperature monitoring devices and check and record temperatures twice daily.[14]

2.3.5 Controlled drugs

Cluttered and overstocked drugs cupboards make it difficult to select the correct medicine.

- Provide a controlled drugs cupboard large enough to meet the dispensary's needs.
- Arrange the stock so that it is well spaced and easily seen.

2.3.6 Waste and returns

Returned or expired medicines may be confused with medicine stock if they are stored in the same area of the dispensary.

- Returned or expired stock should be stored in a separate section of the dispensary to differentiate it clearly from medicine stock.

[13] See *WHO PQS catalogue*, Section E004.

- If possible, keep waste and returns in a separate room away from the main stock, or in clearly designated cupboards, or under bench areas.
- Sharps bins should also have a designated area for storage and should be separated from stock.

2.3.7 Location and arrangement of stock

For operational efficiency, and to avoid dispensing errors, it is essential to be able to find medicines easily.

- As far as possible, use a simple alphabetical A–Z stock storage system organized by proprietary or generic name as appropriate.
- TTSPPs and controlled drugs should be similarly arranged.

2.3.8 Separation of stock

Stock that is unseparated and muddled can increase the risk of selection errors.

- The use of shelf dividers helps ensure that different products, strengths and formulations do not become mixed and confused.
- The use of sloping pull-out drawers that enable stock to be seen and easily retrieved may also help reduce selection errors.

2.3.9 Patient areas

Disorderly queuing can cause confusion and distract both patients and staff. Confidentiality is essential when pharmacists talk to patients about their medicines. Waiting patients should be kept away from the counter so that they cannot overhear these discussions.

- Use effective signage so that patients know where to go to hand in or collect prescriptions, or to ask for advice. This leads to shorter queues, less confusion and improved communication. It also reduces pressure on pharmacy staff and allows them to concentrate without interruption.
- Use techniques such as different coloured flooring and counter dividers to demarcate areas where confidential discussion takes place.
- Locate patient waiting areas away from areas where consultations take place. Provide adequate seating for the elderly and disabled.

2.3.10 Supervised consumption

Some medicines – for example antibiotics for treating tuberculosis, or drugs given to substance misusers – should be self-administered by the patient in the

pharmacy environment in order to confirm that they have been taken, or to prevent misuse or sale on the black market. In such cases patient privacy and staff security will need to be enhanced.

- Ideally, provide a separate area for supervised consumption and other activities associated with substance misusers e.g. needle exchange.
- Consider the provision of security measures to protect staff, such as panic buttons and closed-circuit television (CCTV).
- Consider having higher counters in these areas; this enhances security without compromising communication between staff and patients.
- Ensure sharps bins are inaccessible to other patients.

2.4 Building procurement

The chosen procurement route for a building project should fit the client's long-term objectives; these include speed, cost and quality of construction, risk mitigation, asset ownership, financing, and specific project constraints. In order to choose the most appropriate procurement route, the client may need to obtain independent advice.[14]

2.4.1 Preparing and agreeing the brief

It is important that the client understands enough about warehouse design and operations to be able to communicate the initial requirements to the team at the time of appointment, in the form of a *strategic brief*. This document describes the requirements for which the building design provides the solution; it is crucial to the success of the project. The brief evolves over the life of the project and requires specialist input from the consultant team.

The stages of brief development are described in **Annex 1**.

2.4.2 Appointing and working with the consultant team

Good buildings are built when a knowledgeable client is matched with a team of expert consultants, all parties communicate effectively and timely decisions are taken so as to meet predefined project milestones. It is the client's responsibility to select and appoint the right consultants for the job – on a large lump-sum project this will include an architect, structural engineer, services engineer, and probably a cost consultant. The consultant team for other procurement routes may be smaller, depending on the contractual arrangement with the design-and-

[14] This section has been developed, with permission, from guidance material at: http://www.designingbuildings.co.uk/

build or public–private partnership (PPP) contractor. For a warehouse project of significant size, the consultant team must include members with expertise in this specialist field. At this stage it is also good practice to appoint the commissioning team who are responsible for bringing the building into operation immediately after handover; ideally this team should also be involved in the design process, including the design risk assessment.

2.4.3 Design risk assessment

The design process should include a fully documented *design risk assessment* exercise. The purpose of this exercise is to identify risks and eliminate them wherever possible; where elimination is not possible, residual risks should be reduced and managed.[15]

Both the construction and operation of warehouses and pharmacies expose workers to health and safety risks. Day-to-day operational risk mitigation is one of the key responsibilities of the building management team. However, decisions made by the design team may also have long-term consequences for safe operation and maintenance of the building and will certainly affect the safety of workers during the construction phase. For example, all construction activities and many post-construction maintenance operations require working at height, with the consequent risk of injury from falls and from falling objects. It is the responsibility of the design team to consider both how design decisions can reduce the need for these activities and to provide adequate protection for workers when these tasks cannot be avoided. Careful consideration of design risk issues throughout the design process is likely to lead to a building that is both easier to construct and safer and less expensive to operate.

2.4.4 Choosing a procurement route for new buildings

The client and consultant team must agree on the appropriate procurement route at an early stage. **Annex 2** describes three major types of building contract; there are numerous variants of each of these alternatives.

- *Lump sum:* This is the traditional procurement route. The client is responsible for developing the design brief and the client's appointed design team is responsible for the building design; the contractor then builds this design for an agreed sum.
- *Design and build:* The client remains responsible for the design brief; some or all of the design responsibility is passed to the contractor.

[15] http://www.designingbuildings.co.uk/wiki/Risk_assessment describes risk assessment practice in the United Kingdom.

- *Design, build, finance and operate*: This route is typified by a PPP arrangement; the client defines a design brief or a service level requirement; all responsibility for facility design, construction and day-to-day operation is shifted to the contracted party.

Each route has its advantages and disadvantages. In all cases, effective contract management requires clients and their advisers to have a good knowledge of the relevant contractual procedures and a clear understanding of the responsibilities and duties of the parties to the contract.

2.4.5 Choosing a procurement route for building alterations or refurbishment

For projects involving the refurbishment or alteration of an existing building, both the lump sum and design-and-build routes can be followed. The PPP approach might also be suitable, provided the PPP provider has access to a suitable warehouse property portfolio.

2.4.6 The client's role in tendering

A tender is an offer for the supply of goods or services made by a prospective contractor in response to an invitation to tender. The client has a central role to play in this process.

Invitation to tender

Depending on the size of the project and the chosen procurement route, the invitation to tender might be for one single contract or for a series of subsidiary contracts. For example, there might be a main construction contract (perhaps including design by the contractor), supplemented by separate contracts for the demolition of existing buildings on the site and for the design, installation and commissioning of specialist equipment, such as cold rooms to be installed after the building's shell has been completed.

There are numerous approaches to tendering, but it is common practice for the client to require prospective tenderers to respond to a published advertisement by completing a prequalification questionnaire; in addition there may be pre-tender interviews. This process enables the client to prepare a shortlist of contractors with relevant experience and expertise and it reduces inefficiency and wasted effort. The alternative is an open tender process, but this can result in an excessive number of tender offers, some of which will come from wholly unqualified contractors.

An invitation to tender might include:

- a letter of invitation to tender
- the form of tender

- description of the scope of the works
- preliminaries; this is a document which describes the method and circumstances of the works – for example, restrictions on working hours – which may affect the offer price
- contract conditions
- a tender pricing document
- a drawing schedule
- design drawings
- specifications
- the design risk assessment
- criteria to be used for tender evaluation and selection of the successful bidder
- process for reporting tender results.

Ideally, tender documents should be broken down into a series of clearly defined packages (even if there will only be one main contract), each with its own design drawings and specifications suitable for issue to potential subcontractors by the main contractor. This makes it easier for the contractor to price the work and easier for the client to compare tender offers.

Queries and clarifications

There are likely to be mid-tender discussions with the bidders to clarify issues that might otherwise lead to inaccurate tenders. Adequate time needs to be allowed for this process so that the problems raised are fully resolved and the necessary changes are made to the tender documents; the resulting tenders will be better and more accurate and this is likely to save time and money later on.

It is important that every clarification and amendment is sent to every tenderer. It is equally important not to reveal any confidential information divulged to the team during discussions with individual contractors.

Tender submission

At the end of the designated tender period the tenderers will submit their offers. The precise content of the information submitted will vary considerably depending on the procurement route and the tender requirements, but it must include a completed tender return form, a pricing document, details of the construction programme, details of the project management structure and key project personnel. In addition, tenderers should provide supporting material, such as plant and labour resources, and references. The complete package of materials must be sufficient to enable the client to evaluate the tender.

Tender evaluation

The client's tender board will evaluate the tenders received, preferably against predefined selection criteria.[16] It may be necessary to conduct further interviews and negotiations with the preferred bidder, resulting in further adjustment of the tender documents and the submission of a revised tender.

Two-stage tendering

Two-stage tendering allows early appointment of a contractor, before completion of all the information that the tenderers need in order to offer a fixed price.

In the first stage, a limited appointment is agreed, allowing the contractor to begin work. In the second stage, a fixed price is negotiated for the contract. Two-stage tendering is often used for design-and-build projects. In this case, the contractor will tender a fee for designing the building and provide a schedule of rates that can be used to establish the construction price during the second-stage tender.

2.4.7 The client's role during the construction stage

The construction stage starts when the contractor takes possession of the site from the client in order to carry out the works described in the construction contract. When these works are complete, the client's contract administrator certifies that the work is complete and the site is handed over to the client.

Generally, construction does not begin immediately after the contractor has been awarded the contract, but is preceded by a mobilization stage. During this stage the contractor plans the works, places subcontracts, manages specialist design, carries out necessary surveys and so on.

The client's chief responsibilities during the construction phase include:

- attending formal site meetings;
- making timely decisions on any proposed design changes, cost savings and additional expenditure to the extent that these issues arise;
- making interim payments to the contractor in accordance with the contract conditions, against valuations submitted by the contractor and checked by the contract administrator.

The final payment to the contractor is generally made up to a year after handover at the end of a "rectification period", during which the contractor remains responsible for dealing with any defects that may arise.

[16] The lowest priced offer is not always the best offer.

2.4.8 Commissioning and handover

The handover of the building to the client takes place once the contract administrator has confirmed that the works defined in the contract are sufficiently complete to enable the client to occupy and operate the facility. At this point the client must receive all the information needed to operate the building safely and effectively, including the operation and maintenance manual – see Technical Supplement: *Maintenance of storage facilities*.

Having accepted the site from the contractor, the client then has to prepare the building for occupation and operation. As noted in section 2.4.2, the details of this procedure should be agreed early on in the project planning stage and the commissioning team should be nominated so that they can participate in the design process.

2.5 Procuring cold rooms and freezer rooms

Cold rooms and freezer rooms may be procured as component elements of a new building project. They may also be installed in an existing warehouse, either to replace time-expired equipment, or to meet a new need. In both these situations it is important to follow a systematic procurement process, similar to the one described above, in order to ensure that suitable equipment is specified and that it is correctly installed and commissioned. The WHO PQS website includes a set of specifications and verification protocols which can assist with this task.[17] These documents cover panel-based rooms that are erected inside a new or existing building enclosure. In very large cold stores, the insulated enclosure may also form the outer envelope of the building. Guidance on these larger structures has been produced by the Thermal Panel Manufacturers Association.[18]

[17] http://apps.who.int/immunization_standards/vaccine_quality/pqs_catalogue/categorypage.aspx?id_cat=15 under 'category documentation'.

[18] Thermal Panel Manufacturers Association. *General specification for the design and construction of cold store envelopes incorporating prefabricated insulating panels*. September 2006 (http://www.tpma.org.za/Images/Pdf%27s/GENERAL%20SEPCIFICATION1.pdf).

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Annex 1

Briefing documents

Briefing documents evolve over the life of a project and require specialist input from the consultant team. An experienced client may be able to prepare a detailed brief at a very early stage, without the need for a great deal of further development. On the other hand, an inexperienced client may need the help of an independent client adviser to prepare a strategic brief; this can then be developed further with the help of the consultant team[19].

A1.1 Statement of need

A statement of need is the client's very first attempt to describe the possible requirements. This may be drawn up before any final decision has been taken to proceed with the project, or to define precisely what form the project might take.

A1.2 Strategic brief

The strategic brief is written by the client and provides sufficient information about the project to allow the appointment of a suitable consultant team.

The strategic brief is then further developed by the client with the benefit of feedback from the consultant team. The brief will then describe the client's requirements in sufficient detail for feasibility studies and option appraisals to be carried out.

A1.3 Project brief

The project brief is a development of the strategic brief and is the key document upon which the design will be based. It evolves through the project brief stage and the concept design stage with the benefit of information gained from consultations with the client and other stakeholders and ongoing design development. It is "frozen" at the end of the concept design stage and any further changes are subject to formal change control procedures.

The project brief is a formal statement of the objectives and functional and operational requirements of the finished project. It should be sufficiently detailed to enable the project team to prepare detailed designs and specifications; it is an essential reference for the team.

[19] Heavily adapted, with permission, from material at http://www.designingbuildings.co.uk relating to brief development.

In the case of *design and build* or *PPP* contracts the project brief is a key component of the project execution plan. This is further developed at tender stage into an output-based specification, a document which focuses on the client's desired outputs in business terms, rather than providing a detailed technical specification of how the service is to be provided; this allows providers to propose innovative solutions that might not have occurred to the client.

Annex 2

Alternative contracts

This Annex describes three forms of building procurement contract, with risks and responsibilities passing increasingly from the client to the contractor.[20]

A2.1 Lump sum contract

A lump sum contract is the traditional means of procuring construction, and it remains the most common form of construction contract. Under a lump sum contract, a single "lump sum" price for all of the works is agreed before the works begin, although this figure can vary, as described below. A truly fixed-price contract would not necessarily be in the interests of the client as it would require the contractors to price risks over which they may have no control, and which might not arise.

A lump sum contract is generally appropriate where the project is already well defined at the time when tenders are invited, and subsequent design changes are unlikely. This means that the contractor is able to accurately price the risk they are being asked to accept. Lump sum contracts are less suitable where speed is important, or where the nature of the works is not well defined.

A lump sum contract does not give all the project risk to the contractor, but it does give the client some certainty about the likely cost of the works. However, the price of a lump sum contract can change and there are mechanisms for varying the contract sum, as follows:

- *Variations:* These are changes in the nature of the works. Most contracts will contain provision for the contract administrator to issue instructions to vary the design, quantities, quality, sequence or working conditions.
- *Relevant events:* A relevant event may be caused by the client (for example failure to supply goods or instructions), or may be a neutral event (such as exceptionally adverse weather) and may result in a claim for loss and expense by the contractor.
- *Provisional sums:* An allowance for a specific element of the works that is not defined in enough detail for tenderers to price.

[20] Adapted, with permission, from material at http://www.designingbuildings.co.uk relating to building contracts.

- *Fluctuations:* A mechanism for dealing with inflation on projects that may last for several years. The contractor bases the tender on current prices and the contract terms make provisions for the contractor to be reimbursed for price changes over the duration of the project.
- *Other payments:* These include fees for building inspections and payments to sub-contractors and suppliers.

The better defined the works are when the contract is agreed, the less likely it is that the contract sum will change.

A2.2 Design and build

Design and build is a generic term describing a procurement route in which the main contractor is appointed to design and construct the works. This is different from the traditional lump sum contract, described above.

Design and build can appeal to clients as it gives a single point of responsibility for delivering the entire project. Some consider that it is only appropriate for simple projects, where design quality is not the main consideration.

The contractor can be appointed to carry out all of the design work. Alternatively, if the client wishes to have greater influence over the design, a concept design and outline (or performance) specification can be prepared by a consultant employed by the client; the contractor is then appointed to complete the design and carry out the construction.

Contractors may use their own in-house designers to design the building, or they can appoint consultant designers. Alternatively, the client's own designers can be re-employed by the contractor to complete the design.

If the contractor is appointed at the outset of the project he or she can contribute to the development of the design from the beginning. Typically this involves a two-stage process. In the first stage, the contractor is selected on the basis of a fee, preliminaries, overheads and profit. The contractor then works with the design team (who may be employed either by the contractor or by the client at this stage) to develop the design. On the basis of this design, a fixed price is negotiated for the construction stage.

Design and build contracts can be awarded on a fixed-price, lump-sum basis. However, price certainty is then dependent on not making any design changes. Such changes may be expensive because the prices charged by the contractor for those changes will no longer be subject to competition. It is vital therefore that the client gives careful consideration to the preparation of employer's requirements. If they have not appointed their own design team, they may wish to appoint independent client advisers to help them prepare this document. Similarly if the clients' original design team is transferred to

the contractor during the construction stage, the client may want to appoint an independent client adviser to review the contractor's design proposals, administer the contract and monitor works on site.

A2.3 Design, build, finance and operate

An example of a design build finance and operate procurement route is a public–private partnership.

A single contractor, with design, construction and facilities management expertise, as well as funding capability, is appointed to design and build the project and then to operate it for a period of time. The contractor finances the project and leases it to the client for an agreed period (perhaps 30 years) after which the development reverts to the client.

As this is a very long-term relationship, entered into before any design work is undertaken, it is extremely important that the clients define their requirements very carefully, in particular the quality of service that is required and how it will be judged. A great deal of risk is given to the contractors; however the price they offer will reflect this risk.

Revision history

Date	Change summary	Reason for change	Approved

Supplement 3

Estimating the capacity of storage facilities

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

Annex 9: Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products

May 2015

Contents

Abbreviations

EEFO	Earliest-Expiry-First-Out
FIFO	First-In-First-Out
IFRC	International Federation of Red Cross and Red Crescent Societies
ISO	International Standards Organization
MSF	Médecins Sans Frontières
SIA	Supplementary Immunization Activity
SKU	Stock-keeping unit
TTSPP	Time and Temperature-Sensitive Pharmaceutical Product
UPC	Universal Product Code
VEN	Vial, Essential, Nonessential

Acknowledgements

The author of this document is Andrew Garnett, an independent consultant, London, UK.

Glossary

ABC analysis: Tool for reviewing stock movement, which categorizes items by the volume and value of consumption during a specific period of time, usually one year. Class A items – 10 to 20 percent of items, representing 75 to 80 percent of expenditures – are mostly high-volume, fast-moving medicines. Class B items are usually 10 to 20 percent of items, and 15 to 20 percent of expenditures. Class C items often represent 60 to 80 percent of the items but only about 5 to 10 percent of the total expenditures; these are the low-volume, slow-moving items. Thus, class C is a good place to look for items that might not be needed in stock at all times. See also *VEN analysis*.

Controlled or hazardous products: TTSPPs and other products with high illicit value: poisons, narcotics, psychotropic products, inflammable or explosive substances and radioactive materials.

Gross storage capacity: The gross free volume of a load support system available for storing SKUs. This volume is measured between the shelves of a shelving unit, or between the support beams of a racking system.

Insulated shipper: A single-use insulated passive container, containing coolant, typically used to distribute TTSPPs by road or air transport.

Inventory turnover: A measure of the number of times inventory is sold or used in a time period such as a year. The equation for inventory turnover equals the cost of goods sold divided by the average inventory. Inventory turnover is also known as inventory turns, stockturn, stock turns, turns, and stock turnover.

Net storage capacity: The total volume available for storing TTSPPs, taking account of the type of load support system employed (floor-standing pallets, adjustable pallet racking, shelving units or cabinet). Net storage capacity is calculated by multiplying the gross storage capacity of the load support system by the utilization factor (less than one) that can be achieved for the chosen SKU type.

Pallet: Wooden or plastic platform designed to be lifted by pallet jack or forklift truck. Typically used for storing and handling tertiary cartons.

Pharmaceutical product: Any product intended for human use or veterinary product intended for administration to food producing animals, presented in its finished dosage form, that is subject to control by pharmaceutical legislation in either the exporting or the importing state and includes products for which a prescription is required, products which may be sold to patients without a prescription, biologicals and vaccines. Medical devices are not included[1].

[1] Definition from WHO/QAS/08.252 Rev 1 Sept 2009. *Proposal for revision of WHO good distribution practices for pharmaceutical products – Draft for comments*.

Primary container: Bag, blister pack, strip, bottle, cartridge, vial, ampoule, prefilled device, plastic dispenser, tube, single dose container or the like containing tablet(s), capsule(s), liquid preparation or the like.

Refrigeration equipment: The term 'refrigeration' or 'refrigeration equipment' means any equipment whose purpose is to lower air and product temperatures and/or to control relative humidity.

Secondary pack or carton or market package: The package presentation intended for the end user (e.g. bottle + cap liner + dose cap + leaflets + carton) but not including packaging used solely for transport purposes (e.g. *Tertiary carton* or *Insulated shipper*). The secondary pack may contain multiple units of product.

Standard Operating Procedure (SOP): A set of instructions having the force of a directive, covering those features of operations that lend themselves to a definite or standardized procedure without loss of effectiveness. Standard operating policies and procedures can be effective catalysts to drive performance improvement and improve organizational results.

Stock-keeping unit (SKU): In the field of inventory management, a code number, typically used as a machine-readable bar code, assigned to a single item of inventory. As part of a system for inventory control, the SKU represents the smallest unit of a product that can be sold from inventory, purchased, or added to inventory. Applied to wholesale, retail, or production operations, the SKU can assist in monitoring transactions, tracking customer spending patterns, controlling inventory and purchasing, and providing information about pricing[2], for example via its Universal Product Code (UPC). In the context of this Technical Supplement, and depending on the level in the supply chain, an SKU may be a complete pallet, a tertiary carton, a secondary carton or a primary container.

Temperature-controlled: Includes any environment in which the temperature is actively or passively controlled at a level different from that of the surrounding environment within precise predefined limits.

Temperature-modified: Includes any environment in which the temperature is predictably maintained at a level different from that of the surrounding environment, but is not actively or passively controlled within precise predefined limits.

Tertiary pack or carton: The pack/carton that contains a number of secondary cartons; usually constructed of corrugated fibreboard. *Note:* the tertiary carton

[2] Source: http://www.britannica.com/EBchecked/topic/1242199/SKU

is not the same as the insulated shipper used for international air shipment of TTSPPs, although the insulated shipper may contain one or more of these cartons.

Time and temperature sensitive pharmaceutical product (TTSPP): Any pharmaceutical good or product which, when not stored or transported within pre-defined environmental conditions and/or within pre-defined time limits, is degraded to the extent that it no longer performs as originally intended.

Utilization factor: The percentage of the total volume available for storing TTSPPs that can reliably be achieved in practice, taking account of the types of stock-keeping unit (SKU), the types of load support system and the stock management systems used in the store.

VEN analysis: Method for categorizing stock as vital (V), essential (E), or nonessential (N). This system is sometimes modified to two categories – V and N. VEN analysis is often used to prioritize procurement when not enough funds exist to purchase all items requested. The system can also help determine which items should be kept in stock and which can be ordered when needed. See also *ABC analysis*.

1. Introduction

This technical supplement has been written to amplify the recommendations given in Section 3.1 to 3.4 of WHO Technical Report Series No. 961, 2011, Annex 9: *Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products*[3]. Related topics are covered in the following Technical Supplements:

- *Design of storage facilities.*
- *Maintenance of storage facilities.*
- *Qualification of temperature-controlled storage areas.*
- *Security and fire protection in storage facilities.*

1.1 Requirements

Pharmaceutical warehouses and other related storage facilities need to be of an appropriate size to store sufficient TTSPPs and other products to meet demand, taking account of the following factors:

a. The frequency of supply from product manufacturers and/or from higher level warehouses or storage facilities;
b. Levels of safety stock to be held for each product line stored;
c. Frequency of onward delivery to lower level stores or health facilities;
d. Patient demand for each product line, taking account of seasonal and other fluctuations in consumption.
e. Seasonal re-supply factors, such as road closures caused by flooding and the like.

In the case of an existing storage facility, decisions regarding factors a, b and c are in turn affected by the actual storage capacity of the building and the opportunities available for reorganization or expansion.

1.2 Objectives

The objective of the Technical Supplement is to provide guidance on how to meet the above requirements. The document only covers the process of determining the *net storage capacity* required; it does not cover the related process of determining the gross capacity of the storage area and the size of loading bays, packing areas, administrative areas and the like. This is part of the

[3] http://apps.who.int/medicinedocs/documents/s18683en/s18683en.pdf

subsequent building design process, described in the companion supplement: *Design of storage facilities*.

The supplement borrows from, and updates, the methodolgy described in a 1993 WHO document, *How to estimate warehouse space for drugs*[4]. It describes a way of establishing the minimum net capacity of a store and for calculating the net capacity of sub-stores within such a store; for example, cold rooms.

On a continuing basis, the methodology may be used to assist with the planning of forthcoming purchases and deliveries so as to ensure that they do not exceed available warehouse capacity. This on-going review process is particularly important for health programmes undergoing rapid growth. The collected data may also be used to check the capacity of existing stores when supply circumstances change. Finally, the data may also be used to assess transport volumes and to check that adequate temporary storage space is available at ports and airports when deliveries arrive.

1.3 Target readership

The supplement provides guidance aimed at more senior operations staff. Principally these will be the owners and operators of warehouses, pharmacies and other buildings used to store TTSPP's and those responsible for property development and property acquisition on behalf of owners and operators. It will also be of value to those responsible for preparing a brief for the medical warehouse design team when designing or procurring storage facilities.

[4] WHO/DAP/93.3

2. Guidance

Correct estimation of the net volume of TTSPPs, general pharmaceuticals and other related supplies is the critically important first step in designing or procuring a warehouse. It is also essential information for estimating the volume of goods flowing into and out of the facility so that transport requirements can also be calculated. Without these data it is impossible to determine how large a building is required, or to estimate the associated TTSPP cold storage capacity needed within the warehouse. Similar net volume data are also needed to calculate realistic storage requirements for smaller facilities, such as hospital pharmacies or health centres, and also to determine the capacity of refrigerators and freezers in these facilities.

This supplement provides an introduction to some of the concepts involved, outlines the key decisions that should be made and identifies the data that need to be collected. The basic questions that have to be answered in order to size a pharmaceutical warehouse or store can be summarized as follows:

- Which products are to be stored?
- How many units of each product must be stored?
- What is the product's unit volume in the SKU type applicable to this particular storage level (e.g. carton, case, pallet, etc.)?
- What is its ABC and/or VEN rating?
- At what temperature must it be stored?
- Under what security regime must it be stored (e.g. normal security, controlled or hazardous)?
- Does it have an expiry date?

The ABC or VEN rating of the product needs to be recorded because this will affect the final physical layout of the building and the sub-areas within the store – for example 'A' or 'V' rated products tend to be fast-moving lines and some or all of the stock must be readily accessible for efficient order picking. Similarly, products without an expiry date do not necessarily have to be stored in First-In-First-Out (FIFO) order, but could be block stacked or stored on double-deep or drive-in racking to make the most efficient use of storage space. See

companion technical supplement: *Design of storage facilities*. This is in contrast to products with an expiry date which have to be stored in Earliest-Expiry-First-Out (EEFO) order.

2.1 Associated materials and equipment

None required.

2.2 Inventory management concepts

There is a great deal of excellent information available on the subject of inventory management. See for example MDS-3. *Managing access to medicines and health technologies, Chapter 23: Inventory management*[5]. A good understanding of this topic is a necessary precondition for sizing a pharmaceutical store[6]; decisions and assumptions have to be made about the frequency with which the store will be resupplied with goods, the frequency with which these goods will be distributed from the store, or, in the case of a pharmacy or health facility, the rate at which they will be dispensed. Combined with ABC and/or VEN analysis and related policy decisions on the desired service level – the probability that the store will be able to satisfy a medical request involving a particular product[7] – these decisions in turn affect the levels of safety stock to be held in the store. Use and distribution of products is also categorized by the level of care (e.g. hospital, health centre, health post); storage volume estimates also have to take this factor into account.

Whenever an inventory management system is designed or restructured, safety stock policy is an important consideration. The policy on safety stock may differ at each level of the system, between products, or between different facilities at the same level (depending on VEN and ABC classification systems, lead times, and consumption patterns). The objective is to provide maximum service levels throughout the supply system with minimum necessary total safety stock.

Figure 1 illustrates the principles of the 'ideal' inventory control model. In this ideal model, pharmaceuticals are issued in response to demand, but stockouts are not permitted; the stock on hand steadily declines until the point at which an order must be placed.

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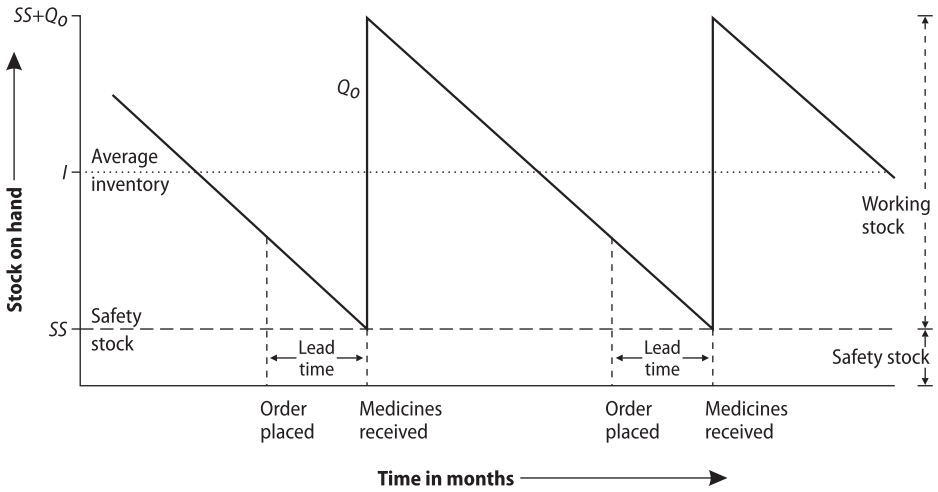
[5] http://www.msh.org/sites/msh.org/files/mds3-ch23-inventorymgmt-mar2012.pdf

[6] The material in the remainder of section is a slightly adapted quotation from MDS-3.

[7] 100 percent service level is desirable, at least for vital items; setting lower goals might be reasonable for nonessential medicines and supplies.

Figure 1
The ideal inventory control model



Source: MDS-3: Figure 23-3

The stock on hand consists of two components: the working stock (WS) and the safety stock (SS). In the ideal model, the supplier performs according to plan, the shipments arrive on time, the quantity ordered (Qo) is received, and the inventory level returns back to its starting maximum point (Qo + SS). Working stock varies from zero to the quantity ordered and represents the stock used to satisfy demand between deliveries. Note that in the ideal model, the average working stock is half of the order quantity:

$$\textit{Average working stock}\ (WS) = \tfrac{1}{2}\ Qo$$

The average inventory (I) or average stock on hand is the safety stock plus the average working stock:

$$I = SS + \tfrac{1}{2}\ Qo$$

When medicines are used at a constant rate, the line in Figure 1 representing stock on hand declines with a constant slope.

In order to reduce the average inventory and thereby reduce the inventory-holding costs – and by extension the size of the required storage facility – the working stock, the safety stock, or both can be lowered. Large, infrequent orders lead to high average inventory levels. The average working stock can be reduced by placing smaller orders more frequently. The average inventory can also be reduced by cutting the safety stock, but this method increases the chance

of stockouts. Alternatively, inventory-holding costs may be reduced through improved storekeeping practices and by better financial management – for example by bulk purchasing.

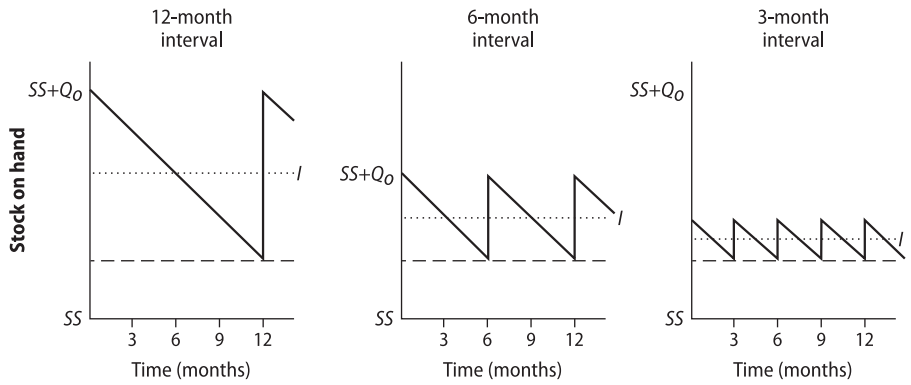
As illustrated in Figure 1, any inventory control model used to manage purchasing must address the following issues –

1. *Safety stock* – how much stock will be kept in reserve to prevent stockouts;
2. *Reorder frequency* – the period of time between each order for an item (also known as the procurement period);
3. *Reorder quantity* – the number of units specified when an order is placed.

In addition, *storage capacity* – the amount of space available for storage – needs to be considered when determining target stock levels and ordering and replenishment frequency.

The policy on reorder frequency has a major influence on average stock levels and inventory-holding costs, as well as on service level. Figure 2 shows how a simple change in reorder interval has a dramatic effect on the average inventory held in a store. The ability to control the reorder interval is one of the key levers available to a warehouse manager in the complex process of balancing incomming and outgoing stock and fluctuating demand levels.

Figure 2
The ideal inventory control model and the effect of reorder interval



Key: I = average inventory Q_O = order quantity SS = safety stock

Source: MDS-3: Figure 23-4

Clearly the ideal model shown above is not an accurate depiction of reality. The actual flow of product into and out of a store is likely to be much lumpier. Some of the reasons for this are as follows:

- Staggered reorder deliveries for different products and/or suppliers;
- Fluctuating demand leading to unequal distributions;
- Seasonal factors;
- Disease outbreaks.

More sophisticated procurement and reordering strategies can be used to help resolve some of these problems, to the extent that the local context allows.

For all the reasons described above, an essential first step in sizing any pharmaceutical store is a clear understanding of current inventory management policies. A failure to appreciate the implications of these policies may radically affect the ability of the store to operate efficiently and may lead to the procurement of a building which is either too small or unnecessarily large. Equally, a systematic analysis and review of current practices can generate substantial cost savings. For example, the increased procurement costs associated with shortening the supply interval might be outweighed by lower building construction or warehouse rental costs, reduced inventory holding costs and reduced expiry due to faster inventory turnover.

Do not attempt to finalize the sizing of a pharmaceutical warehouse until all parties involved have agreed and understood the physical and operational implications of the following:

- The procurement and supply context;
- The applicable inventory management policies;
- The way in which both of these are likely to change over the foreseeable future.

2.3 Collecting product data

Although good data are available on the volume-per-dose and weight of individual vaccine products and associated injection and waste management equipment, collecting similarly detailed information for general pharmaceutical products and related supplies remains a challenge. It is highly unlikely that data on all products will be available. Accordingly the most effective strategy is to concentrate on collecting information on those products that represent a large physical volume and are the fastest moving items – using the principle of ABC analysis, these 'A' classified products will typically represent about 80% of throughput.

2.3.1 Vaccines

In countries where vaccines are stored and distributed as part of an integrated pharmaceutical supply chain these products can represent a significant proportion of total TTSPP volumes[8]. In the field of vaccine logistics, extensive information is available on the volume-per-dose of individual products[9]. These data are used by a number of related tools, enabling logisticians to estimate the required volume per recipient for any specific vaccine schedule[10]. Vaccine volume calculation and the associated sizing of cold chain equipment requirements is now a relatively straightforward task. For both routine and supplementary (campaign) immunization the schedule is fixed at national level, and the target populations, coverage and wastage rates are known to a reasonable approximation. In addition there is only a limited range of products. The WHO prequalified vaccine list contains some 35 vaccines in 213 product/presentation combinations[11]; only a proportion of these combinations are widely used. The list for immunization syringes and safety boxes is also short and data on these products are similarly held on a WHO website[12]. An alternative data source is the UNICEF *Cold Chain Weight and Volume Calculator*[13]. This is restricted to vaccine products supplied by UNICEF Supply Division. However it has the advantage that it includes data on the volume of insulated shipping containers.

2.3.2 General pharmaceuticals, including non-vaccine TTSPPs

Demand for general pharmaceuticals, including non-vaccine TTSPPs, is not as predictable as the demand for vaccines. Quantification of requirements is a specialised topic on which much guidance is available – see for example MDS-3. *Managing access to medicines and health technologies, Chapter 20: Quantifying pharmaceutical requirements*[14].

Estimation is typically based on consumption or morbidity data. Order quantities can then be calculated based on the use classification and stock management principles outlined in Section 2.1. Unfortunately current quantification methodologies and tools only concentrate on estimating the

[8] Many countries still operate a separate vaccine supply chain.

[9] See the WHO vaccine database at: http://www.who.int/immunization_standards/vaccine_quality/PQ_vaccine_list_en/en/index.html

[10] See for example the EVM Assistant tool and user guide at: http://www.who.int/immunization/programmes_systems/supply_chain/evm/en/index3.html

[11] WHO vaccine database, accessed January 2014.

[12] See the WHO PQS database and catalogue at: http://apps.who.int/immunization_standards/vaccine_quality/pqs_catalogue/

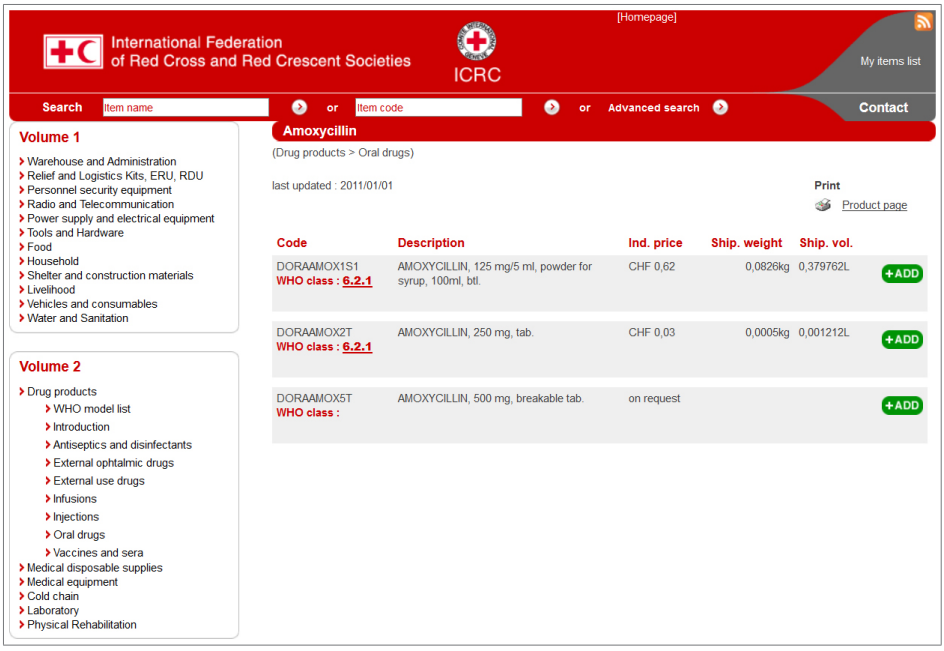
[13] http://www.unicef.org/supply/files/Cold_Chain_Weight_and_Volume_Calculator.xlsm

[14] http://www.msh.org/sites/msh.org/files/mds3-ch20-quantifying-mar2012.pdf

number of doses – or physical units – required for each product; they do not specifically capture physical characteristics (package dimensions and weight) as an aid to logistics planning.

The 2013 WHO Model List of Essential Medicines (adults and children) contains well over 300 generic products, themselves available from multiple manufacturers and in multiple formats[15]. The UNICEF Supply Catalogue likewise lists a large number of pharmaceutical products, as does MSF. None of these sources provides any data on physical packed volumes. However, the IFRC catalogue does list shipping weights and volumes for many products and the catalogue entries are cross-referenced to the WHO list – see Figure 3.

Figure 3
IFRC catalogue page



Source: http://procurement.ifrc.org/catalogue/detail.aspx?productcode=DORAACSA

In addition, the UNICEF Catalogue uses an icon classification system which is helpful in allocating products to specific storage zones based on temperature and/or security and/or safety considerations. Table 1 shows a sample.

[15] In 1977 WHO listed 220 essential medicines; this had risen to 340 by 2010. Source: WHO.

Table 1
UNICEF catalogue icons

Icons	Category	Detailed description
	Temperature considerations	**Cold Chain temperature requirements:** Constant temperature between +2 to +8°C at all levels from manufacturer to the end user. **Cool Chain temperature requirements:** Constant temperature between +8 and 15 ˚C at all levels from manufacturer to the end user. **Controlled Room Temperature**[16]: Temperature between +15 ˚C and + 25 ˚C. Pharmaceutical products: Unless specified as having cold chain or cool chain requirements, should be kept at controlled room temperature and not above 25 °C or in a freezer during transport and storage; unless otherwise specified on the label. **Vaccines:** Sent directly from manufacturers. **Polio vaccines** should be stored between –15 to –25 °C at primary cold chain stores. At the lower service delivery point, they should be stored between +2 to +8 °C. **All other vaccines** should be stored between +2 to +8 °C at all levels. **Diagnostics:** Should be kept at controlled room temperature and not above 25 °C or in a freezer during transport and storage; unless otherwise specified on the label.
	Narcotic/ psychotropic substance	Narcotic and or psychotropic substances, which require import authorisation. i.e. Diazepam, Phenobarbital, Morphine, Ketamin, as well as related kits (IEHK kit, suppl.1a-drugs, Midwifery kits, suppl.1a-drugs, Obstetric, surgical kit, suppl.1a-drugs).
	Hazardous materials	Items that are classified as hazardous materials (dangerous goods) are subject to transport restrictions i.e. requiring special labelling and packaging in accordance with international rules on handling and transportation of hazardous materials. Depending on the danger classification, some hazardous materials must be shipped by sea.

[16] The UNICEF catalogue defines controlled room temperature as: *Temperature between 20 ˚C and 25 ˚C. Excursions between 15 ˚C and 30 ˚C and spikes up to 40 ˚C are permitted, as long as they do not exceed 24 hours*. However +15 °C to +25 °C is generally available in most third party warehouses.

Table 1 *continued*

Icons	Category	Detailed description
	Air only	Items requiring cold chain transportation/storage must be sent only by air. Items include vaccines and Oxytocin, and related kits (IEHK kit, suppl.1a-drugs, Midwifery kits, suppl.1a-drugs, Obstetric, surgical kit, suppl.1a-drugs).
	Shelf life	Items with a shelf life.
	Storage considerations	Some items require specific storage conditions.

In the absence of a comprehensive central database of product volumes and weights, the analyst has to rely on those sources that are available. This includes data collected locally from on-site measurement and from the shipping documentation provided by supply agencies, manufacturers and distributors.

For an alternative approach to data collection, refer to the 'Layout planning' section of the JSI document: *Guidelines for Warehousing Health Commodities*.

2.3.3 Volume data and SKU types

It is important to be clear about the type of Stock-keeping Unit (SKU) to which the collected volumetric data applies. In the case of vaccines, there are three 'levels' of SKU that are relevant to warehouse sizing:

a. *Secondary carton:* The first level is the secondary carton[17] which contains the vaccine vials or 'primary containers'.

b. *Tertiary carton:* Some vaccines are supplied in tertiary cartons or cases, each containing a number of secondary cartons; the additional layer means that the volume-per-dose for this SKU type is slightly increased.

c. *Insulated shipping container:* Finally, when vaccines are shipped by air, they are generally packed with coolant in insulated shipping cartons. For ease of bulk handling, some countries choose to store their vaccines at the central warehouse level in these containers. The thickness of the insulation and the space occupied by coolant means

[17] The WHO vaccine database publishes the volume-per-dose in a secondary carton SKU. The database is gradually being extended to include data on tertiary cartons and insulated shipping containers.

that the volume-per-dose for this SKU type can be several times greater than the product's listed volume-per-dose in a secondary carton SKU[18].

If these volumetric differences are not recognized in the process of estimating net storage volume, the size of a cold room calculated on the basis of the published WHO figures will be far too small. Similar volume-per-dose ranges apply to other TTSPPs, especially those that are air-freighted in insulated containers[19].

When carrying out a net volume calculation, do ensure that the dimensional and weight data that are used are correct for the SKU type which will be held in the store.

Larger and bulkier SKUs with greater unit volumes are typically stored and transported at higher levels in the supply chain. When bulk is broken for distribution to peripheral facilities, SKU dimensions and unit volumes will generally be smaller.

2.4 Calculating maximum inventory volumes

Once the relevant SKU volume data have been collected, as described in the previous section, inventory volume calculations for each product can be carried out.

Do make allowances for fluctuations in demand and resupply for individual products. In addition, do make sure that you take account of future programme expansion plans and include an adequate allowance for new product lines, including new vaccine introductions.

2.4.1 Vaccines and related supplies

Vaccine volume requirements can be calculated using one of the WHO Excel tools that have been designed for this purpose – see Tools section. The general principle on which these tools work is described by the formulae below.

[18] For information on shipping container volumes, see also the UNICEF *Cold Chain Weight and Volume Calculator*.

[19] It is possible to ship TTSPPs in actively cooled sea or air containers. In this case, insulated packaging might be unnecessary.

Maximum stored volume of each vaccine used for routine immunization:

$$IV_{max} = (P_{tot} \times \frac{T}{100} \times \frac{1}{R_f} \times \frac{100}{(100-W)} \times \frac{(100+SS)}{100} \times V_{dose} \times D_{series}) \text{ / } 1{,}000{,}000$$

Maximum stored vaccine volume for supplementary immunization activities (SIA):

$$IV_{max} = (P_{tot} \times \frac{T}{100} \times \frac{100}{(100-W)} \times \frac{(100+SS)}{100} * V_{dose}) \text{ / } 1{,}000{,}000$$

Where:

IV_{max} Maximum inventory volume for the specific vaccine, in cubic metres;

P_{tot} Total population: This is used as the basis for standardising a population target for each vaccine;

T Target population percent: This is the percentage of the total population targeted to receive a specific vaccine for a specific immunization purpose. For example, the target population percentage for birth-dose hepatitis B is different from the target population for the same vaccine given to health workers.

R_f Reorder frequency: the number of times that vaccine is scheduled to be received by a store or facility in one year;

W Percentage of vaccine wasted during distribution and delivery: the formula for this term converts the percentage wastage rate for the vaccine into the wastage factor;

SS Safety stock: Expressed as a percentage of the working stock;

V_{dose} Vaccine volume-per-dose in cm^3 is measured at the level of the type of SKU applicable to the store (secondary carton, tertiary carton of shipping container);

D_{series} Number of doses per series as set out in the immunization schedule. When this figure is multiplied by the vaccine volume-per-dose, it gives the volume of packed vaccine for a completed series of immunizations.

Note: When using formula B, review the planning data for future supplementary activities to estimate the worst-case total vaccine volume. This depends on both target population and vaccine volume-per-dose. If deliveries for parallel SIAs coincide, the maximum volumes for each activity must be summed.

The data needed for the storage volume calculations for syringes and sharps safety boxes relate closely to the formulae described above and are calculated within the tools referenced below. The calculation method takes account of the following factors:

- *Vaccine formulation:* oral or injectable; liquid or lyophilized (and requiring a separate reconstitution syringe);
- *Vaccine presentation:* single or multi-dose vials or pre-filled injection device;
- *Safety box capacity:* Number of used syringes or pre-filled devices that can be accommodated into the chosen size of safety box;
- *Syringe wastage:* A small proportion of syringes will be wasted due to breakage or mishandling.

Similar calculations can be carried out for the injection device and waste management needs of other injectable products.

2.4.2 General pharmaceuticals and supplies, including non-vaccine TTSPPs

To calculate maximum net inventory volumes for general pharmaceuticals, use the following formula:

Maximum stored volume for general pharmaceuticals and supplies:

$$IV_{max} = \left(AD \times \frac{1}{R_f} \times \frac{(100+SS)}{100} \times V_{unit}\right) / U$$

Where:

IV_{max} Maximum inventory volume for the specific product line;

AD Annual demand: This is the estimated number of units of the product required per year obtained from the requirements quantification process;

R_f Reorder frequency: The number of times that the product is scheduled to be received by a store or facility in one year;

SS Safety stock percent: Stores must be sized to allow for an appropriate reserve stock; this may vary from product to product depending on its ABC or VEN classification;

V_{unit} Volume-per-unit: Measured in at the level of the type of SKU applicable to the store (primary container, carton, pallet or other SKU); this may be expressed in cm^3 (divisor = 1,000,000), litres (divisor = 1,000) or m^3 (divisor = 1).

U Volume conversion unit: The divisor needed to convert the result into cubic metres.

2.5 Calculating net storage capacity requirements

By the end of the procedure described in Section 2.6, the maximum inventory volume for each product line will have been calculated. However, a figure for maximum inventory volume on its own does not tell you where in the store each product line should be kept, or how much actual space it will actually occupy in the store. In order to establish this it is necessary to classify every product by storage temperature and security category and then to establish the most suitable type of load support system within each of these storage zones.

2.5.1 Classifying products by storage temperature and security category

The first step in the sizing process is to group products in 'families' according to their labelled storage temperature and security regime. Table 2 shows a matrix for establishing the possible combinations, based on the UNICEF catalogue classifications shown in Table 1[20] – not all of these will be relevant in any particular situation. This allocation process has significant implications for the final design of the store. For example, should TTSPP narcotics be stored in a locked or caged off area of the main cold room, or should they be located in a separate secure cold room or in a refrigerator in a separate locked room? The decision will depend partly on the relative volumes involved and partly on a detailed risk assessment of the individual products in the context of the actual operating environment.

In the classification shown below, space has been allowed for products that require a 'normal' level of security, controlled products such as narcotics or poisons which have a high illicit value or are dangerous and must be kept in a secure locked compound, and hazardous products which are inflammable, explosive or radioactive and require special storage conditions, such as an explosion-proof refrigerator or a room with an explosion hatch. Some products may be both 'controlled' and 'hazardous'.

Table 2
Temperature and storage regime 'families'

Temperature	Normal security	Controlled	Hazardous	Controlled and hazardous
Below –25.0 °C				
–15.0 to –25.0 °C				
+2.0 to +8.0 °C				

[20] Other classifications are used. For example, MSF lists five temperature regimes: –15 to 0 °C, +2 to +8 °C, +5 to +25 °C, +5 to +35 °C and +5 to +40 °C (unpublished draft warehouse design guideline).

Table 2 *continued*

Temperature	Normal security	Controlled	Hazardous	Controlled and hazardous
+8.0 to +15.0 °C				
+15.0 °C to +25.0 °C				
Uncontrolled ambient				

When the applicable combinations have been identified, the total net storage volume for each category can be entered in the table above by sorting the cumulative volume data into the relevant categories.

2.5.2 Load support systems

The most common load support systems are shelves (open or closed), floor standing pallets and multi-level pallet racking systems. In addition, secure cupboards may be used for narcotics and hazardous substances and drawers may be used for smaller items. There are also a number of other more sophisticated systems such as flow racking and carousels which can be used to increase picking efficiency. Finally, in smaller facilities, TTSPPs are likely to be kept in refrigerators or freezers rather than in cold stores with bulk storage on shelving or racking. Refrigerators and freezers may be front opening or top opening, so the product may be stored on shelves or in baskets.

Comprehensive guidance on the use and limitations of most types of load support system is given in the JSI document: *Guidelines for Warehousing Health Commodities*.

2.5.3 The utilization factor concept

A refrigerator, a drawer, a shelving bay or a pallet racking bay has a certain gross storage capacity available for storing goods – defined by the length, width and height of the free storage volume, measured inside the cabinet, between shelves, or between racking support members and the like. Only in exceptional cases can this volume be fully occupied by stored product. In practice the available volume has to be modified by a *utilization factor* which will always be less than one. How much less than one depends on a number of additional factors, including:

- *Storage method:* The two basic methods are *fixed* and *fluid*. In fixed-location storage, each (SKU) is always kept in a specific location. No other SKU can be stored in that location, even if the location is empty. In fluid-location storage, any SKU can be assigned to any free location. It is possible to have both fixed and fluid systems

operating in a warehouse simultaneously. In fact, this arrangement is sometimes preferable. A typical arrangement would call for most bulk supplies to be stored on pallets and loose items to be stored on shelves. A fixed-location system is used for items stored on shelves; a fluid-location system is used for the pallets stored on the pallet racks. Table 3 indicates the appropriate use of the two methods[21].

Table 3
Temperature and storage regime 'families'

Type of commodity	Storage method	Example types
Low inventory items stored and issued in smaller packs	Fixed (entire stock kept on shelves)	Specialized medicines
Bulky items stored and issued in complete pallets	Fluid (entire stock kept on pallets)	Equipment
Items contained in large cartons stored on pallets but issued in smaller packs	Fixed (stock to be issued kept on shelves) and fluid (bulk stock kept on pallets)	Essential drugs that are issued by bottles or small packs; condoms

Source: JSI | DELIVER: *Guidelines for Warehousing Health Commodities*. Table 5.

- *Dimensional compatibility:* The way in which the product fits the available storage space. For example a carton that is 35 cm high will make poor use of a shelving bay if the shelves are fixed at 60 cm apart;
- *Space occupied by additional elements:* For example, the volume of the supporting pallet in a pallet racking bay uses a proportion of the available storage volume.
- *Ventilation around the product:* This is a particular requirement in cold rooms where it is necessary to maintain a good airflow to ensure even temperature distribution.
- *Unsuitable zones:* Some parts of the load support system may be unsuitable for storing particular products due to temperature deviations or temperature stratification – see the companion Technical Supplement: *Qualification of temperature-controlled storage areas*.

[21] Adapted from JSI | DELIVER: *Guidelines for Warehousing Health Commodities*.

- *Ease of access:* For example, a health facility refrigerator containing a mix of products may be packed quite loosely so that the health worker can easily access individual products. This reduces effective volume utilization.

2.5.4 Pallet bay calculation

Table 4 shows the six ISO pallet sizes; of these, the EUR-EPAL and the US 40" x 48" are widely encountered. The latter makes particularly efficient use of the space in standard ISO shipping containers. Other non-ISO sizes are also used, including the EURO pallet range.

Table 4
Standard ISO pallets

Dimensions, mm (W × L)	Wasted floor in ISO container	Region where most used
1016 × 1219 (40" x 48")	3.7% (20 pallets in 40 ft ISO)	North America
1000 × 1200	6.7%	Europe, Asia; similar to 40" × 48".
1165 × 1165	8.1%	Australia
1067 × 1067	11.5%	North America, Europe, Asia
1100 × 1100	14%	Asia
800 × 1200 (EUR-EPAL)	15.2%	Europe; fits many doorways

Source: http://en.wikipedia.org/wiki/Pallet

The volume of product that can be stacked on a pallet depends on the size of the pallet, the extent to which the product cartons coordinate with the pallet footprint, and the stacking height. In practice, a reasonable assumption is that a EUR-EPAL can hold an average of about 0.8 m³ and a US 40" x 48", or ISO 1000 mm x 1200 mm pallet, can hold about 1.0 m³. On this basis[22] the following formula can be used to estimate the number of pallet bays required for each of the product lines which will be allocated for pallet storage.

[22] Source: JSI | DELIVER and MSF.

$$N_{pallet} = \frac{IV_{max}}{V_{pallet}}$$

Where:

N_{pallet} Number of pallets required to store the product line;

IV_{max} Maximum inventory volume for product line, in cubic metres;

V_{pallet} Average volume of product per pallet, in cubic metres.

2.5.5 Shelving unit calculation

A reasonable rule is that only half to two thirds of the gross storage capacity of shelving units[23] can actually be occupied by product – a utilization factor between 0.5 and 0.65. When planning a store layout it is safer to adopt the lower figure, although the use of an adjustable shelving system may allow more efficient use of the available volume.

In warehouses, especially those that include pallet racking, the top shelf is often much lower than the ceiling so that storing product at this level is not restricted by ceiling height; instead, the maximum stacking height is restricted by the need to be able to access the product on the upper shelves. If access is from floor level, the height of the top shelf should be no more than 1.7 to 1.8 metres above the floor, and no more than 1.6 to 1.7 metres if the shelves are wider than 600 mm. If access is from a mobile ladder, the maximum shelf height can be increased to about 2.7 metres.

In smaller stores and in walk-in cold rooms and freezer rooms, ceiling height is often restricted and product on the top shelf has to be arranged so that there is space for air circulation above the load.

The following two formulae can be used to assess the length of shelving unit required, in metres, to store a given net volume of product, expressed in cubic metres[24]. The first version is used where ceiling height is restricted; the formula assumes a clearance of 10 cm between the top of the load and the ceiling for air circulation. The second version is used where ceiling height is not restricted; in this case the height of the load placed on the top shelf is assumed to be 40 cm – this figure can be changed.

Shelf unit length (restricted ceiling height):

$$L_{shelf} = \frac{IV_{max}}{(H_{room} - (b + (n \times t) + 0.1)) \times w \times UF}$$

[23] The volume measured between shelves.

[24] The first two calculation methods described below can be found in the WHO EVM Assistant tool.

Shelf unit length (unrestricted ceiling height):

$$L_{shelf} = \frac{IV_{max}}{(H_{unit} + 0.4 - (b + (n \times t))) \times w \times UF}$$

Where:

L_{shelf} Length of shelving unit required to store the product line, in metres;

IV_{max} Maximum inventory volume for the product to be stored, in m^3;

H_{room} Room height, in metres;

H_{unit} Height of shelving unit from floor to top shelf, in metres;

b Height of underside of bottom shelf from floor, in metres;

n Number of shelves;

t Shelf thickness, in metres;

w Shelf width, in metres;

UF Utilization factor (from 0.5 to 0.65).

If standard sized shelving unit bays with a known gross storage capacity are used (including the gross storage volume above the top shelf), an alternative and simpler approach is to use the following formula:

$$N_{bay} = \frac{IV_{max}}{V_{bay} \times UF}$$

Where:

N_{bay} Number of shelving bays required to store the product line;

IV_{max} Maximum inventory volume for the product to be stored, in m^3;

V_{bay} Gross capacity of one shelving bay, in cubic metres;

UF Utilization factor (from 0.5 to 0.65).

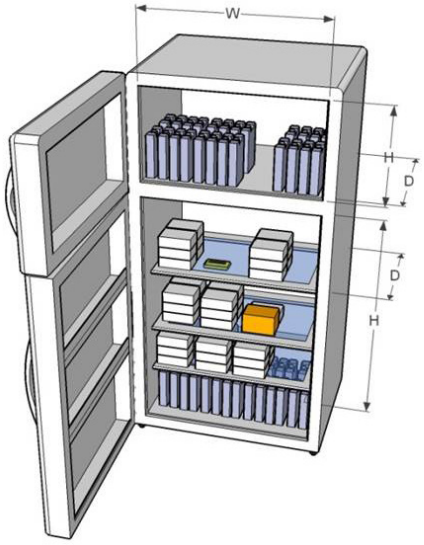
2.5.6 Closed shelving units and safety cabinets

These units are used to store controlled and hazardous products. It is reasonable to apply a utilization factor of 0.5 to the rated capacity of the unit.

2.5.7 Refrigerators and freezers

Data on gross and net storage capacity for WHO prequalified vaccine refrigerators and freezers are published in the WHO *PQS catalogue*. For non-prequalified products, and where manufacturer's data are not available, the method described in Figure 4 can be used.

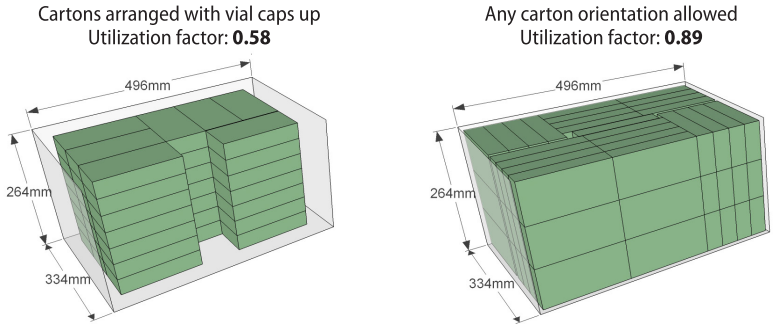
Figure 4
Measuring capacity of a front opening refrigerator



2.5.8 Load optimization tools

Numerous software tools are available, designed to optimize available storage volume on load support systems and in transport vehicles. These tools can also be used to make efficient use of the storage space when stacking pallets, packing shipping cartons, cold boxes and the like – see **Tools** section. Figure 5 illustrates an example of a cold box packing problem, solved by using one of these packages. The calculation produces an image of each packing arrangement, together with the relevant utilization factor.

Figure 5
Cartons of vaccine packed in a prequalified cold box



Many of these tools can handle the optimization of mixed loads – the most sophisticated versions are used to drive robotic pallet stackers.

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- MSF. *Essential drugs: Practical guidelines*. Médecins Sans Frontières. February 2013. http://refbooks.msf.org/msf_docs/en/essential_drugs/ed_en.pdf
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- UNICEF Supply Catalogue
  https://supply.unicef.org/unicef_b2c/app/displayApp/%28layout=7.0-12_1_66_67_115&carea=%24ROOT%29/.do?rf=y
- *WHO Model List of Essential Medicines – current lists*.
  http://www.who.int/medicines/publications/essentialmedicines/en/index.html
- *WHO List of Prequalified Medicinal Products*
  http://apps.who.int/prequal/query/ProductRegistry.aspx
- *WHO PQS catalogue*
  http://apps.who.int/immunization_standards/vaccine_quality/pqs_catalogue/categorylist.aspx
- WHO Technical Report Series, No. 902, 2002. Annex 9. *Guidelines on packaging for pharmaceutical products*
  http://www.who.int/medicines/areas/quality_safety/quality_assurance/GuidelinesPackagingPharmaceuticalProductsTRS902Annex9.pdf
- WHO Technical Report Series No. 961, 2011, Annex 9: *Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical*
  http://apps.who.int/medicinedocs/documents/s18683en/s18683en.pdf

Tools

Load optimization tools:

- Cape Systems. http://www.capesystems.com/index.htm
- CubeIQ. http://www.magiclogic.com/
- CubeMaster Online. http://www.cubemaster.net/Subscription/home.asp
- Iris Pallet. http://www.iris-it.com/en/products/robotics/palletization-software.html
- Logen. http://www.logensolutions.com/default.html
- PLMPack Stackbuilder (freeware). http://stackbuilder.codeplex.com/
- QuickPallet Maker. http://www.koona.com/qpm/
- TOPS Pro and Maxload Pro. http://www.topseng.com/index.html

Quantification tools:

- Center for Pharmaceutical Management, Management Sciences for Health. *Quantimed: Pharmaceutical Quantification and Cost Estimation Tool*. Arlington, VA. 2011. http://www.emtct-iatt.org/wp-content/uploads/2013/02/Quantimed-Pharmaceutical-Quantification-and-Cost-Estimation-Tool.pdf

Vaccine volume calculation tools:

- UNICEF *Cold Chain Weight and Volume Calculator and User Guide*. http://www.unicef.org/supply/files/Cold_Chain_Weight_and_Volume_Calculator.xlsm
- WHO *EVM Assistant tool and EVM Assistant Tool user guide*. http://www.who.int/immunization/programmes_systems/supply_chain/evm/en/index3.html
- WHO *Vaccine volume calculator and User guide*. http://apps.who.int/immunization_delivery/systems_policy/logistics/en/index4.html

Revision history

Date	Change summary	Reason for change	Approved

Supplement 4

Building security and fire protection

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

Annex 9: Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products

May 2015

Contents

Abbreviations

BS	British Standard
CCTV	closed-circuit television
EHS	environmental, health and safety
NFPA	National Fire Protection Association (United States)
SLA	service level agreement
SOP	standard operating procedure
TTSPP	time- and temperature-sensitive pharmaceutical product

Acknowledgements

The author of this document is Dr Clare Barker, Principal Consultant, Fire Engineering Europe, Exova Warringtonfire, England.

Glossary

Controlled or hazardous products: TTSPPs and other products with high illicit value: poisons, narcotics, psychotropic products, inflammable or explosive substances and radioactive materials.

Key fob: A small security device with built-in authentication used to control entry to a building and/or entry through internal doors within a building.

Pharmaceutical product: Any product intended for human use or veterinary product intended for administration to food producing animals, presented in its finished dosage form, that is subject to control by pharmaceutical legislation in either the exporting or the importing state and includes products for which a prescription is required, products which may be sold to patients without a prescription, biologicals and vaccines. Medical devices are not included.[1]

Service level agreement (SLA): A service level agreement or contract is a negotiated agreement between the customer and service provider that defines the common understanding about materials or service quality specifications, responsibilities, guarantees and communication mechanisms. It can either be legally binding, or an information agreement. The SLA may also specify the target and minimum-level performance, operation or other service attributes.[2]

Standard operating procedure (SOP): A set of instructions having the force of a directive, covering those features of operations that lend themselves to a definite or standardized procedure without loss of effectiveness. Standard operating policies and procedures can be effective catalysts to drive performance improvement and improve organizational results.

Third-party accreditation: Accreditation or certification by an organization that issues credentials or certifies third parties against official standards as a means of establishing that a contractor is competent to undertake a specific type of work. Third-party accreditation organizations are themselves formally accredited by accreditation bodies; hence they are sometimes known as *accredited certification bodies*. The accreditation process ensures that their certification practices are acceptable, typically meaning that they are competent to test and certify third parties, behave ethically and employ suitable quality assurance.

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[1] Definition from WHO/QAS/08.252 Rev 1 Sept 2009. *Proposal for revision of WHO good distribution practices for pharmaceutical products – Draft for comments*.

[2] Definition from International Air Transport Association (IATA). Perishable cargo regulations (ePCR) and Temperature control regulations (eTCR) 2013/2014.

Time and temperature-sensitive pharmaceutical product (TTSPP): Any pharmaceutical good or product which, when not stored or transported within predefined environmental conditions and/or within predefined time limits, is degraded to the extent that it no longer performs as originally intended.

1. Introduction

This technical supplement has been written to amplify the recommendations given in WHO Technical Report Series No. 961, 2011, Annex 9: *Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products*.[3]

1.1 Requirements

Ensure that buildings used to store time- and temperature-sensitive pharmaceutical products (TTSPPs) have sufficient security to prevent unauthorized access and to prevent misappropriation of goods.

Ensure that all areas that are used to store controlled or hazardous TTSPPs are:

a. dedicated, securely locked facilities that fully comply with all legislative and regulatory requirements applicable in the country where the store is located;
b. only accessible to authorized staff;
c. protected by automatic intruder and/or fire and smoke, and/or chemical and/or radiological sensor alarm systems appropriate to the type(s) of product being stored;
d. designed to be explosion-proof, where explosive TTSPPs are stored; and
e. continuously monitored by security staff or by a qualified external security company. Continuous monitoring may be on-site or remote.

Provide suitable fire detection and firefighting equipment, including fire hydrants, in all TTSPP storage areas and ensure that:

a. systems and equipment are appropriate for the class of occupancy and product storage arrangements and are approved by the local fire authority; and
b. equipment is regularly serviced in accordance with the equipment manufacturers' recommendations and local regulations.

Follow standard operating procedures (SOPs) for fire prevention, detection and control. Train staff and carry out regular fire drills. Prohibit smoking in all areas.

[3] http://apps.who.int/medicinedocs/documents/s18683en/s18683en.pdf

1.2 Objectives

The objectives of this Technical Supplement are to provide guidance on how to meet the above requirements with regard to building security, fire prevention, fire detection and management of the buildings.

1.3 Target audience

This document is written for managers of buildings used to store TTSPPs, security personnel and the person designated as the "responsible person" who must carry out a fire risk assessment of the premises.

1.4 Associated materials and equipment

None required.

2. Guidance

An effective health service is dependent upon an assured supply of pharmaceutical products many of which have a street value if they are misappropriated. It is essential that compounds in which there are buildings used to store TTSPPs in significant quantities should be adequately protected against fire and theft.

2.1 Site security and emergency access

Compounds containing pharmaceutical stores should be surrounded by perimeter fencing or walls of a suitable height to ensure the security of the grounds and storage buildings against vandalism, theft or arson. If local regulations do not permit perimeter fencing, alternative measures to provide perimeter protection should be taken. There should also be a security gatehouse to monitor vehicles entering and leaving the site. If resources permit, perimeter lighting and monitoring by closed-circuit television (CCTV) should be installed. This is the first level of protection needed to prevent unauthorized access and to prevent theft. Additional levels of security are needed within the individual buildings on the site.

Access roads to all buildings on the site should be provided so that vehicles can deliver goods to the storage facility. Building regulations also require adequate access to a minimum percentage of the building perimeter so that fire and rescue service vehicles can reach the source of a fire; this percentage increases with the aggregate area of the individual building.

2.2 General building security

Windows and doors at ground floor level are most vulnerable and should therefore be fitted with good quality locks. Shutters or fixed security bars are also recommended on windows. Buildings should preferably be protected by an automatic intruder alarm system.

The building should be kept locked and all keys should be kept under close control. Keys should be distributed to nominated keyholders only and regular checks should be made to ensure that they have not been lost. The locks should be of a type whose keys cannot easily be copied, or can only be duplicated with the written authorization of the building manager.

If resources permit, key fob and/or number code entry systems should be used instead of keys. This type of entry system eliminates the need for additional keys to be cut and allows access to be recorded on a computer. This technology also allows lost key fobs to be deleted easily from the system and door codes to be changed regularly.

Where resources permit an audio or video entry system is recommended for additional security.

2.3 Controlled and hazardous substances areas

All areas used to store controlled or hazardous TTSPPs must be securely locked and must fully comply with all legislative and regulatory requirements applicable in the country where the store is located.

These areas should be accessible only to authorized staff and they should be protected by a suitable range of automatic alarm systems appropriate to the types of products being stored and the likely risks. These alarm systems may include intruder detection, fire and smoke detectors, and sensor systems to detect chemical and/or radiological hazards.

Areas used to store potentially explosive substances should be designed to be explosion-proof. All areas should be continuously monitored, as a minumum by security staff by carrying out regular patrols, or by CCTV where resources permit.

2.4 Fire detection systems

Suitable fire protection equipment should be provided in all TTSPP storage areas. It is essential that the following are provided:

- *An automatic fire detection and alarm system:* This should be designed, installed and maintained to the relevant standards.[4]
- *First aid firefighting equipment:* This should include hand-held fire extinguishers selected and maintained to the relevant standards.[4]

To meet the requirements of local building regulations a manual alarm system may be the minimum standard required in warehouses since there is no sleeping risk. However, there are often circumstances in which an automatic fire detection system is needed. For example, this could be needed to compensate for some departure from the guidance in the local building code, or as a component of the operating system for a fire protection system. It may also be needed where a fire could break out in an unoccupied part of the building, which prejudices the means of escape from the occupied parts.

The automatic detection system should be designed, installed and maintained in accordance with the relevant standard.[5] If maintenance of fire detection and firefighting systems and equipment is contracted out, this should be under the terms of a clearly defined service level agreement (SLA).

[4] For guidance see the International Fire Code and the national standards cited in the References section. National standards will always have priority; however American, European or British standards have been widely adopted by many countries that do not have their own standards.

[5] e.g. British Standard (BS) 5839-1 (2013), NFPA 72, or the *International Fire Code*.

2.5 Fire suppression equipment

The following protection systems are desirable where resources allow:

- *An automatic sprinkler system (fire suppression system):* This should be designed, installed and maintained to the relevant standard.
- *A smoke ventilation system:* This may be manually or automatically operated.

2.5.1 Sprinkler systems

An automatic fire suppression system should be provided in accordance with the relevant standards.[6] It is recommended that the system should be installed and maintained by a contractor with appropriate third-party accreditation.

Firefighting water can be supplied from the following sources:

- *City mains water supply:* The agreement of the water authority is usually required for a city mains connection. Where water quality is poor, strainers must be fitted on all connections to the mains supply.
- *Storage tanks:* This can be a pump suction tank, gravity tank or reservoir.
- *Inexhaustible sources:* This includes lakes or rivers.
- *Pressure tanks*.

The relevant hazard classification of the system for use in high bay pharmaceutical warehouses is typically defined as "ordinary hazard" (OH3 (BS EN 12845) or OH2 (NFPA 13)).

Wet pipe sprinklers should be used in high bay warehouses – this means that the sprinkler network is fully charged with water at all times. The use of the alternative, dry pipe, system could result in an unacceptable time delay between the activation of a bulb and the flow of water through the sprinkler head.

Where the goods are stored in pallet racks, the provision of in-rack sprinklers as well as roof level sprinklers is recommended. The sprinkler bulbs in the in-rack sprinkler heads activate at a much lower temperature than those at roof level; consequently the firefighting water is discharged in a more localized area. This means that the fire can be contained with less water damage than would be expected from the discharge of roof level sprinklers.

In cold climates, the installation may require protection against freezing if the pipework passes through unheated spaces. Freeze-protection can be

[6] E.g. BS EN 12845, NFPA 13, or the International Fire Code.

achieved using antifreeze liquid or electrical trace heating. Where sprinklers are installed in cold rooms or freezer rooms, dry pendant drops should be used. With this arrangement, sections of dry pipe serve the relevant risk area and the actual flow valves are located outside the cold store. This prevents the water in the system from freezing.

2.5.2 Smoke ventilation systems

Automatic smoke vents are generally provided to assist means of escape from the building. By venting smoke build-up at high level, the occupants can escape from the building underneath the smoke layer in reasonably safe conditions. Additional manually operated smoke vents are generally provided to aid the fire and rescue service with smoke clearance once the fire has been extinguished.

Where both sprinkler systems and smoke vents are provided in a building the interaction between them must be carefully considered. Research by Factory Mutual showed that the provision of automatically operating smoke vents can cause delays in the operation of sprinkler systems. This is because the automatic smoke vents open when triggered by smoke, whereas sprinklers operate when heat is detected. As smoke is generally detected more quickly than heat, Factory Mutual concluded that sprinklers would perform more effectively if there were no vents. Their reasoning was that the building would fill with smoke; this in turn creates low oxygen conditions which limits combustion, allowing the sprinklers to extinguish the fire more effectively.

However, where life safety is the predominant concern and a smoke control solution is used to protect the escape routes within a building, current guidance requires the smoke vents to operate automatically; the vents will therefore activate before the sprinkler system.

Alternatively, if the fire service response time is short, and the sprinkler system is provided with fast response heads, the smoke ventilation system may be activated by the flow switch in the sprinkler supply.

2.6 Compartmentation

Buildings are often divided into compartments enclosed in fire-resisting construction; this approach provides passive fire protection by inhibiting the spread of fire within the building. In order to comply with local building regulations, the size of individual compartments may have to be limited. Compartment size is determined by the overall size of the building, the number of storeys, and whether or not an automatic sprinkler system is provided.

In the United Kingdom, for example, single storey storage buildings which are not provided with sprinklers can have a maximum area of 20 000 m^2; where sprinklers are provided the maximum area is unlimited.

2.7 Fire prevention, training and control procedures

Preventing fires from occurring is as important as having properly working fire safety systems to deal with a fire incident. The main objective is to create an operating environment in which fires are prevented from starting in the first place. If a fire does break out, the aim is to prevent it from developing beyond a very minor event.

2.7.1 Risk assessment

The first step in fire prevention is to assess the risks and record them in a risk register.[7] This requires reviewing and assessing the means by which a fire might start and spread, the potential consequences and the available approaches to mitigate the risk. This includes assessing day-to-day operations, risks associated with periodic building and maintenance work and those arising from installing new equipment, or adopting new or changing technologies.

2.7.2 Fire prevention

Set out below are the principal actions that need to be taken to monitor the behaviour of workers and prevent fires from occurring:

- Smoking is one of the greatest fire risks and it should be prohibited in all buildings and workplaces. Where there is no legal prohibition, smoking should only be allowed in designated smoking areas and fire-safe ashtrays and bins should be provided.
- Enforce good housekeeping practices; this includes implementing routines for the regular removal and disposal of waste.
- Establish and maintain out-of-hours inspection and security procedures, including means of preventing arson.
- Carry out routine checks, inspections, and tests, including monitoring the maintenance of heat generating equipment that could cause fires, chafing of cables, self-heating of cables due to electrical resistance and checks on fuel supplies and storage.
- Issue and control work permits and associated procedures.
- Instruct and supervise contractors and subcontractors carrying out construction and maintenance operations within the building.
- Avoid conditions leading to gas and dust explosion hazards.
- Maintain integration with other systems (e.g. ventilation, communications).

[7] See for example: Watson N, Serumaga B, McCord J, Inglis A (2013).

2.7.3 Fire safety training

All employees should be given fire safety training by a person who is competent in the subject and who understands effective training methods. If relevant expertise is not available within the organization, an independent expert – for example from the fire service – should be engaged to provide training.

Fire safety training should start with induction training on the first day of appointment of new staff. There should be refresher training at least once a year to ensure that all staff are familiar with the fire precautions for the workplace and are reminded of the actions to take in an emergency. More frequent training should be given where there is a high turnover of staff, or a high risk of fire.

All staff, including part-time staff, security staff, cleaning staff and contractors should be trained and instructed in:

a. risk awareness;
b. smoking policy;
c. basic fire prevention;
d. good housekeeping;
e. the fire routine:
   - actions to be taken when a fire is discovered or an alarm is heard;
   - knowledge of the escape routes and exits, especially those not in regular use;
   - raising the alarm and the location of alarm indicator panels;
   - arrangements for calling the fire and rescue service;
   - special provisions for assisting disabled people;
   - location of firefighting equipment;
   - selection and use of firefighting equipment, including hand-held firefighting equipment (on larger premises it may be appropriate to train specific staff instead of all staff);
   - the importance of fire doors and the need to close all doors at the time of a fire and/or on hearing the fire alarm;
   - process shutdown and shutting down of non-essential equipment, stopping machines and processes and isolating power supplies if appropriate;
   - evacuation procedures.
f. Incident reporting procedures, including for "near miss" events and false alarms. A "no blame" reporting culture should be encouraged.

Supervisory and other staff who have specific responsibility for fire safety should receive detailed instruction in their own duties and appropriate

refresher training at least once, and preferrably twice a year. Staff with particular responsibilities are likely to include:

- department heads;
- fire marshals or fire wardens;
- floor supervisors;
- security staff (including night security patrols);
- engineering and maintenance staff;
- receptionists and telephonists.

2.7.4 Fire control procedures

Follow the SOP for housekeeping – see **Annex 1**.

Follow the SOP for routine inspection of fire safety installations– see **Annex 2**.

Follow the SOP for fire drills– see **Annex 3**.

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- World Health Organization. Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical pharmaceuticals. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-fifth report. Geneva: World Health Organization; 2011: Annex 9 (WHO Technical Report Series, No. 961; http://apps.who.int/medicinedocs/documents/s18683en/s18683en.pdf, accessed 15 February 2015).

Annex 1

SOP: Fire safety housekeeping

A1.1 Policy and objectives

A1.1.1 Policy

In order to protect property and life, SOPs should be followed for fire prevention, detection and control.

A1.1.2 Objectives

This SOP describes the housekeeping routines that should be followed to manage fire safety and to prevent fires from occurring within the building.

A1.2 Responsibility

The Fire Safety Manager or Environmental Health and Safety (EHS) Manager has day-to-day responsibility for the prevention of fires.

Note: It is essential to designate a Fire Safety Manager or EHS Manager to oversee the activities described in this SOP.

A1.3 Associated materials and equipment

None.

A1.4 Procedure

A1.4.1 Reducing ignition sources

Identify and control potential ignition sources.

Responsibility: Fire Safety or EHS Manager

a. Smoking is not permitted in any areas of the building. Control illicit smoking by appropriate management, or consider providing smoking areas outside the building, provided with fire-safe ashtrays and bins.
b. Naked flames, e.g. candles, or heaters using naked flames are not permitted.

c. Hot works[8] will only be carried out after a permit to work has been issued.
d. Food and drink preparation and consumption will only be carried out in rest areas designated for this purpose.
e. Misused or faulty electrical equipment should be reported immediately and replaced or removed.
f. Overheated or worn cables should be repaired or replaced.
g. Lighting displays, e.g. halogen lights, should not be placed near flammable material.
h. In areas where flammable, volatile or explosive materials are stored, ensure that electrical fittings are suitable for the risk classification.
i. All equipment should be installed, maintained, used and managed in the appropriate manner by competent personnel. This should be supported by staff training.

A1.4.2 Reducing fuel load

The amount of combustible material should be reduced, or stored more safely.

Responsibility: Fire Safety or EHS Manager

a. Reduce the fire load. For example replace bottled gas heating with electric heating sources, or reduce the amount of bottled gas stored within the building.
b. Store goods in an appropriate manner, e.g. in dedicated storerooms.
c. Store and use highly flammable substances safely, and store in appropriate containers.
d. Control the amount of rubbish and how it is stored. Store rubbish in a safe location away from buildings, preferably in a designated area. Rubbish bins within the building should be emptied every day.
e. Remove redundant services from voids as these can constitute a significant fire load.

A1.4.3 Maintenance of fire protection measures

Check regularly that fire protection measures are available at all times and will be able to carry out their function in a fire.

[8] *Hot work* is any process that can be a source of ignition when flammable material is present or can be a fire hazard, regardless of the presence of flammable material in the workplace. Common hot work processes are welding, soldering, cutting and brazing. When flammable materials are present, processes such as grinding and drilling become hot work processes.

Responsibility: Fire Safety or EHS Manager

a. Keep escape routes clear at all times. Goods and equipment must not be stored on escape routes or allowed to block exits, as this provides an unwanted fire load and a potential ignition source and constitutes a life safety risk.
b. Maintain door locks, panic bars and automatic door release mechanisms so that they open easily in an emergency.
c. Do not obstruct fire alarm call points, portable fire extinguishers or fire hydrants with stored goods, machinery or parked vehicles.
d. Ensure that all fire safety equipment (fire alarms, emergency lighting, and fire extinguishers) are maintained and tested in accordance with the relevant standard by competent personnel – see companion SOP: Routine inspection and maintenance of fire safety installations (Annex 2).
e. Certain parts of the building may contain flammable elements which can contribute to fire spread, such as insulated core panels surrounding cold rooms and other temperature-controlled areas. Panels should be checked regularly and any damaged panels repaired.
f. Goods should not be stored close to windows. If the building has a sprinkler system, goods should not be stacked higher than the maximum height recommended in the applicable standard.

A1.5 Related documents

- BS 5306-3: 2009: Fire extinguishing installations and equipment on premises. Commissioning and maintenance of portable fire extinguishers. Code of practice.
- BS 5839-1:2013. Fire detection and fire alarm systems for buildings. Code of practice for design, installation, commissioning and maintenance of systems in non-domestic premises.
- BS EN 12845: 2004 +A2: 2009. Fixed fire-fighting systems. Automatic sprinkler systems. Design, installation and maintenance.
- BS EN 1838:2013. Lighting applications. Emergency lighting.
- International Air Transport Association (IATA). 2013/2014. Perishable cargo regulations (ePCR) & temperature control regulations (eTCR) http://www.iata.org/publications/Pages/temperature-control-regulations.aspx

- National Fire Protection Agency (NFPA) 13-2013: Automatic sprinkler systems. 2013 Edition.
- National Fire Protection Agency (NFPA) NFPA 72-2013: National fire alarm and signalling code. 2013 Edition.

Note: The documents listed above relate to standards and practices in the United Kingdom and the United States. Where other standards apply, adapt the references accordingly.

Annex 2

SOP: Routine inspection and maintenance

A2.1 Policy and objectives

A2.1.1 Policy

To protect property and life, SOPs should be followed for fire prevention, detection and control.

A2.1.2 Objectives

This SOP describes the routine inspections that should be carried out on any fire safety installations provided in the building.

The fire safety equipment within the building, including passive fire protection provisions, should be inspected frequently. Most of the inspection can be undertaken by suitably trained personnel; however if installations such as automatic sprinkler systems and smoke ventilation systems are provided then a formal service level agreement (SLA) should be made with the installer to conduct regular inspection and testing in accordance with the applicable standards.

A2.2 Responsibility

The Fire Safety or Environmental Health and Safety (EHS) Manager has day-to-day responsibility for the prevention of fires.

Note: It is essential to designate a Fire Safety Manager or EHS Manager to oversee the activities described in this SOP.

A2.3 Associated materials and equipment

None.

A2.4 Procedure

A2.4.1 Daily inspections

Responsibility: Fire Safety or EHS Manager

a. Check automatic fire detection and alarm systems to ensure that:
   – the control panel indicates normal operation;

- if a fault is indicated it should be logged and action taken to rectify it;
- any fault recorded on the previous day has received attention.

b. Check emergency and escape lighting systems to ensure that:
- every lamp is lit, if it is a maintained system;
- the control panel for any central battery system or generator indicates normal operation;
- any fault found is logged and action taken to rectify it.

c. Check sprinkler system to ensure that:
- there is continuity of the connections between the alarm switch and the control unit and between the control unit and the fire and rescue service;
- the water level and air pressure are correct in any pressure tank that provides a duplicate supply;
- any necessary corrective actions are taken.

d. Fire doors that are held open by automatic release mechanisms should be released daily.

e. Check every point where a portable fire extinguisher or hose reel is usually located. Missing or damaged fire extinguishers or hose reels should be replaced or repaired immediately. Any extinguishers used in a fire, or for training, or which are otherwise discharged, should be recharged immediately.

f. Document findings and corrective or preventive actions if applicable.

A2.4.2 Weekly inspections

Responsibility: Fire Safety or EHS Manager

a. Check automatic fire detection and alarm systems to ensure that:
- The control equipment is able to receive a fire signal and to initiate the evacuation procedure, recording which trigger device has been used.
- Any standby batteries are in good condition and the fuel, oil and coolant levels of any standby generators are correct and topped up if necessary.

b. Check the sprinkler system to ensure that:
- water and air pressure gauge readings on installations, trunk mains and pressure tanks, and water levels, in elevated private reservoirs, rivers, canals, lakes, water storage tanks, etc., meet the design criteria and that all gauge readings and levels are recorded;

- each water motor alarm has been sounded for at least 30 seconds;
- automatic pumps start when the water pressure is reduced to the specified level;
- for automated pumps powered by a diesel engine:
  - the fuel and oil levels of the engine meet the design and/or manufacturer's specification;
  - the oil pressure, flow of cooling water through open-circuit cooling systems, or the water level in the primary circuit of closed-circuit cooling systems, all meet the design and/or manufacturer's specification;
  - the engine restarts using the manual start test button;
- the electrolyte level and density of all lead acid cells meet the design and/or manufacturer's specification. If the density is low the battery charger should be checked for efficient operation and if the charger is working correctly the affected cells should be replaced;
- the stop valves which control the flow of water to the sprinkler systems from the water supply are in the correct position and any monitoring systems are working correctly;
- there is continuity of connection between the alarm switch and the control unit and between the control unit and the fire and rescue service for alarm systems which are automatically monitored by the emergency service provider;
- trace heating systems provided to prevent freezing in the sprinkler systems are functioning correctly.

c. Check any smoke control systems provided for means of escape by simulating actuation of the system. Ensure that any fans and powered exhaust ventilators operate correctly, smoke dampers close, natural exhaust ventilators open, automatic smoke curtains move into position, etc.

d. Check fire hydrants once a week to ensure that there are no obstructions that may impede access, that the indicator plates are in position and visible and that the isolating valves are locked open.

e. Document findings and corrective or preventive actions if applicable.

A2.4.3 Monthly inspections

Responsibility: Fire Safety or EHS Manager

a. Check the fire detection and alarm system by carrying out the following actions:

- Simulate failure of the normal power supply and start up the standby generator, allow it to energize the system for at least one hour and monitor the system for any malfunctioning caused by use of the generator.
- Restore the normal power supply and then test the charging arrangements for the generator starting battery. If they are not functioning correctly then appropriate action should be taken.
- Top up oil and coolant levels and fill the fuel tanks.

b. Check the emergency lighting system by carrying out the following actions:
   - Simulate failure of the supply to the normal lighting and inspect all luminaires and exit signs to ensure they are functioning correctly.
   - If the standby supply is from a generator with back-up batteries, a test should be carried out to determine whether all luminaires and exit signs function correctly, even if the generator is prevented from starting.
   - Repair or replace any luminaires or exit signs that do not function correctly.
   - Restore supply to the normal lighting and ensure that:
     - indicator lamps or devices to self-contained luminaires or internally illuminated exit signs show that the normal supply has been restored;
     - indicator lamps or devices to central battery systems show that the normal supply has been restored, and that the charging arrangements are functioning correctly;
     - ihe charging arrangements for any battery for starting a generator are functioning correctly;
     - oil and coolant levels are topped up and fuel tanks filled.

c. Check hose reels visually once a month to ensure there are no leaks and that drum assemblies are free to rotate on their spindles.

d. Check the operation of fail-safe mechanisms on automatic opening doors, either by "breaking out" the doorset, i.e. pushing it open manually, or simulating failure of the mains supply. Record the results of the test and repair or replace any faulty doors.

e. Check doors on hold-open devices by simulating failure of the mains power supply or operation of the fire alarm system. Record the results of the test and repair or replace any faulty hold-open devices.

f. Check all emergency and panic escape devices on escape doors (especially on external doors not used for other purposes) to ensure ease of operation and opening of the door, this can be affected by weather conditions.
g. Document findings and corrective or preventive actions if applicable.

A2.4.4 Three-monthly inspections

Responsibility: Fire Safety or EHS Manager

a. Check the smoke control system by simulating actuation, testing each zone separately.
b. Ensure that all fans and powered exhaust ventilators operate correctly, and that smoke dampers close.
c. Document findings and corrective or preventive actions if applicable.

A2.4.5 Six-monthly inspections

Responsibility: Fire Safety or EHS Manager

a. Inspections and tests should be carried out by competent personnel on the following:
   - fire detection and alarm system;
   - sprinkler system (if provided);
   - emergency and escape lighting systems.
b. Log any defects, take any remedial action and obtain test certificates.
c. Check fire doors to ensure the following:
   - heat-activated seals and smoke seals are undamaged;
   - door leaves are not structurally damaged or excessively bowed or deformed;
   - gaps between the door leaf and frame are not so small as to be likely to bind, or so large as to prevent effective fire and smoke sealing;
   - hanging devices, securing devices, self-closing devices and automatic release mechanisms are operating correctly.
d. Document findings and corrective or preventive actions if applicable.

A2.4.6 Yearly inspections

Responsibility: Fire Safety or EHS Manager

a. Inspections and tests should be carried out by competent personnel on the following:

- fire detection and alarm systems;
- self-contained luminaires with sealed batteries, if more than 3 years old;
- sprinkler systems;
- smoke ventilators and smoke control systems;
- fire hydrants;
- portable fire extinguishers – apply dated stickers to confirm extinguishers have been checked – see typical sticker layout in Figure A2.1.
- hose reels.

Figure A2.1
Typical sticker for recording checks made on a portable fire extinguisher

b. Log any defects, take any remedial action and obtain test certificates.
c. Document findings and corrective or preventive actions if applicable.

A2.5 Related documents

- BS 5306-1: 2006: Code of practice for fire extinguishing installations and equipment on premises. Hose reels and foam inlets.
- BS 5306-3: 2009: Fire extinguishing installations and equipment on premises. Commissioning and maintenance of portable fire extinguishers. Code of practice.

- BS 5839-1:2013. Fire detection and fire alarm systems for buildings. Code of practice for design, installation, commissioning and maintenance of systems in non-domestic premises.
- BS 7036 series: 1996: Code of practice for safety at powered doors for pedestrian use.
- BS 7273-4: 2007: Code of practice for the operation of fire protection measures. Actuation of release mechanisms for doors.
- BS 8214: 2008: Code of practice for fire door assemblies.
- BS 9990: 2006: Code of practice for non-automatic fire-fighting systems in buildings.
- BS EN 12101: Smoke and heat control systems.
- BS EN 12845: 2004 +A2: 2009. Fixed firefighting systems. Automatic sprinkler systems. Design, installation and maintenance.
- BS EN 1838:2013 – Lighting applications. Emergency lighting.
- NFPA 13-2013. Automatic sprinkler system. 2013 Edition.
- NFPA 72-2013. National fire alarm and signalling code. 2013 Edition.

Note: The documents listed above relate to standards and practices in the United Kingdom and the United States. Where other standards apply, adapt the references accordingly.

Annex 3

SOP: Fire drills

A3.1 Policy and objectives

A3.1.1 Policy

To protect property and life, SOPs should be followed for fire prevention, detection and control.

A3.1.2 Objectives

This SOP describes the procedure to be followed when conducting fire drills to ensure that the building can be evacuated quickly and safely in the event of a genuine fire.

A3.2 Responsibility

The Fire Safety or Environmental Health and Safety (EHS) Manager has day-to-day responsibility for the prevention of fires and the management procedures related to fire safety.

Note: It is essential to designate a Fire Safety Manager or EHS Manager to oversee the activities described in this SOP.

A3.3 Associated materials and equipment

Stopwatch.

A3.4 Procedure

A3.4.1 Conducting test evacuations

Responsibility: Fire Safety or EHS Manager

a. Evacuation procedures should be tested at least once, preferably twice, per year.
b. A full evacuation of the entire building should be carried out at least once a year.
c. Any deficiencies observed in the fire safety management procedures should be remedied and, if necessary, the written instructions should be amended.

d. The Fire Safety Manager must identify the purpose of the test evacuation and explain it to the staff so that it can be assessed.

e. The objectives of a test evacuation are to:
   - test management procedures;
   - provide practical training to staff;
   - establish whether training is satisfactory;
   - identify weaknesses in emergency communications procedures and systems;
   - identify positive and negative reactions of staff with designated responsibilities;
   - assess the reliability of equipment;
   - rehearse joint action with the fire and rescue service.

f. Test evacuations should not be carried out at regular times; otherwise staff may become prepared for them.

g. Each test evacuation should presume a different scenario so that different situations can be dealt with.

h. Prior notice of test evacuations should only be given to those who have designated responsibilities for monitoring the test (e.g. personnel witnessing the exercise and reporting on the positive and negative aspects) so that they are as realistic as possible. People undertaking this monitoring task should not be otherwise involved in the evacuation (e.g. should not be given fire marshal duties).

i. Continuous monitoring of the evacuation is essential, by video recording if possible, to allow a detailed comparison between planned and actual actions and to assist with training.

j. Where possible test evacuations should include the procedures for evacuating disabled people.

k. Fire safety systems should be employed as part of a test evacuation to check whether such systems are creating unforeseen difficulties and whether software-controlled procedures (i.e. those used to switch on fans, open vents, release doors and sound alarms) are operating as intended.

l. Carry out a full debrief at the end of the exercise so that lessons can be learned and changes made to the evacuation procedures if necessary.

m. Document findings and corrective/preventive actions if applicable.

A3.5 Related document

- BS 9999: 2008. Code of practice for fire safety in the design, management and use of buildings.

Note: The document above relates to standards and practices in the United Kingdom. Where other standards apply, adapt the reference accordingly.

Revision history

Date	Change summary	Reason for change	Approved

Supplement 5

Maintenance of storage facilities

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

Annex 9: Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products

May 2015

Contents

Abbreviations

CM	corrective maintenance
EHS	environmental, health and safety
IPM	inspection and preventive maintenance
MoU	Memorandum of Understanding
PM	preventive maintenance
SLA	service level agreement
SOP	standard operating procedure
TTSPP	time- and temperature-sensitive pharmaceutical product

Acknowledgements

The author of this document is Andrew Garnett, an independent consultant, London, England.

Glossary

Design–build: A project delivery system used in the construction industry. The design and construction services are contracted by a single entity known as the design–builder or design–build contractor, typically for an agreed lump-sum price.

Facility management: The professional management of building infrastructure. Responsibilities of the facility manager include day-to-day operation, space allocation and management of changes to the building, management of health and safety, fire safety, security, maintenance, testing and inspection, cleaning, contingency/disaster planning and tendering for outsourced contracts relating to any of these activities.

Maintenance management: The administrative, financial, and technical framework for assessing and planning building maintenance operations on a scheduled basis; a subset of facility management.

Pharmaceutical product: Any product intended for human use or veterinary product intended for administration to food producing animals, presented in its finished dosage form, that is subject to control by pharmaceutical legislation in either the exporting or the importing state and includes products for which a prescription is required, products which may be sold to patients without a prescription, biologicals and vaccines. Medical devices are not included.[1]

Practical completion: In most construction contracts, the date at which the architect or contract administrator certifies that the works have been completed, and the end-user is able to occupy the building. Some minor works, called snagging items, may remain and must be completed by the contractor within a reasonable time period.

Refrigeration equipment: The term "refrigeration" or "refrigeration equipment" means any equipment whose purpose is to lower air and product temperatures and/or to control relative humidity.

Service level agreement (SLA): A service level agreement or contract is a negotiated agreement between the customer and service provider that defines the common understanding about materials or service quality specifications, responsibilities, guarantees and communication mechanisms. It can either be legally binding, or an information agreement. The SLA may also specify the target and minimum level performance, operation or other service attributes.[2]

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[1] Definition from WHO/QAS/08.252 Rev 1 Sept 2009. *Proposal for revision of WHO good distribution practices for pharmaceutical products – Draft for comments*.

[2] Definition from International Air Transport Association (IATA). *2013/2014 Perishable cargo regulations (ePCR) & temperature control regulations (eTCR)*.

Standard operating procedure (SOP): A set of instructions having the force of a directive, covering those features of operations that lend themselves to a definite or standardized procedure without loss of effectiveness. Standard operating policies and procedures can be effective catalysts to drive performance improvement and improve organizational results.

Time and temperature-sensitive pharmaceutical product (TTSPP): Any pharmaceutical good or product which, when not stored or transported within predefined environmental conditions and/or within predefined time limits, is degraded to the extent that it no longer performs as originally intended.

Uniclass: Unified Classification for the Construction Industry, published in 1997 in the United Kingdom, is a classification scheme for the construction industry. It is intended for organizing library materials and for structuring product literature and construction project information.

1. Introduction

This Technical Supplement has been written to amplify the recommendations given in section 3.10 of WHO Technical Report Series No. 961, 2011, Annex 9: *Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products*.[3] It does not specifically deal with emergency maintenance or contingency planning. Related topics are covered in the Technical Supplement: *Maintenance of refrigeration equipment*.

1.1 Requirements

Implement a planned preventive maintenance programme to ensure that storage buildings and building utilities are well maintained. Keep records to demonstrate compliance with the programme.

1.2 Objectives

The objective of this Technical Supplement is to provide guidance on how to meet the above requirements. The document covers the maintenance of building sites, building structures and building services. It does not cover the maintenance of refrigeration equipment and cold store enclosures contained within those structures. This topic is covered by the companion Technical Supplement: *Refrigeration equipment maintenance*.

1.3 Target readership

This supplement provides guidance aimed at more senior operations staff. Principally these will be the owners and operators of warehouses, pharmacies and other buildings used to store time- and temperature-sensitive pharmaceutical products (TTSPPs). Where appropriate the activities described in this supplement should be assigned to a qualfied maintenance manager or facility manager.

[3] http://apps.who.int/medicinedocs/documents/s18683en/s18683en.pdf

2. Guidance

Maintenance of buildings, when effectively carried out, ensures that the structure and its contents are protected from damage and loss. In the case of a large pharmaceutical warehouse, the value of the pharmaceutical products that are stored in the facility may well exceed the value of the building itself. Unfortunately, maintenance is often neglected and underfunded in the public sector. Defects accumulate and, if they are dealt with at all, this takes place in a piecemeal fashion.

This document focuses on planned maintenance. It gives a broad overview of building maintenance principles and it outlines some of the challenges that have to be overcome in order to implement a high standard of maintenance practice. It is not intended to be a comprehensive technical guide; readers are encouraged to consult the reference sources for a fuller understanding of the topic.

2.1 Associated materials and equipment

Suitable checklists and inspection and access equipment will be required to carry out the inspection activities advocated in this supplement. The tools and materials for carrying out actual maintenance tasks are outside the scope of this document.

2.2 What is maintenance and why is it important?

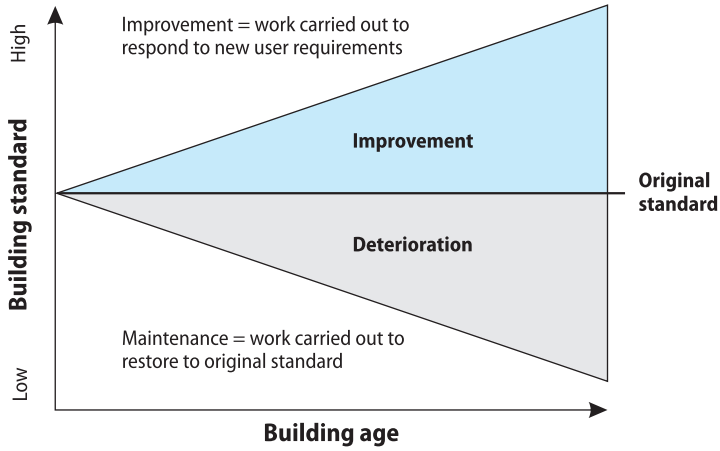
The purpose and scope of building maintenance has been defined in many ways. A good general definition is that:

> Building maintenance is the totality of all actions that keep a building functioning effectively.[4]

All buildings deteriorate over time. Maintenance, if well carried out, rectifies this deterioration and returns the building to its original as-built state. Maintenance helps protect the financial assets tied up in the building; it is not the same as improvement. The purpose of improvement is to alter and/or extend the building in ways which respond to changing user requirements and this may increase its value. Figure 1 illustrates this distinction.

[4] Wood B. Building maintenance. Oxford: Wiley-Blackwell; 2009.

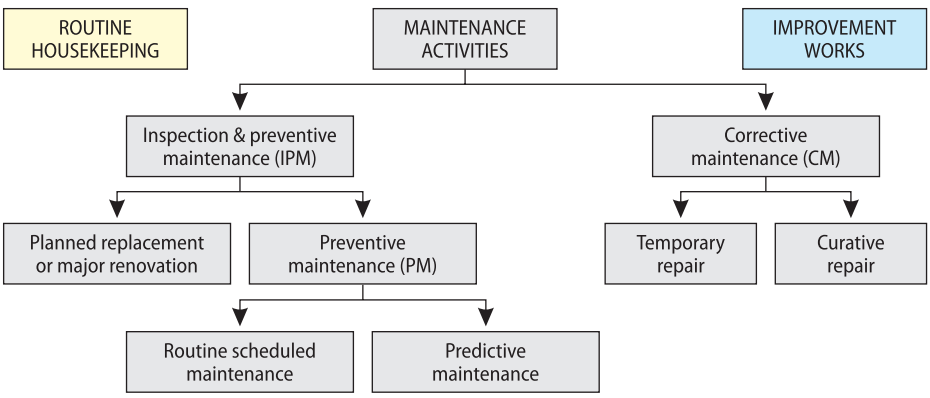
Figure 1
Relationship between improvement and maintenance



Adapted from Miles and Syagga, (1987) and Stanford, (2010).

Figure 2 illustrates the various types of maintenance and their relationship to related activities. Maintenance can be divided into two major categories: inspection and preventive maintenance (IPM), and corrective maintenance (CM). Note that housekeeping actions such as cleaning and pest control, even though they can and should be planned, are generally regarded as part of routine day-to-day operations rather than maintenance – a clean building is not necessarily a well-maintained building. As noted above, improvement work is also a separate activity.

Figure 2
Types of maintenance



Adapted from Stanford (2010).

To be effective, both financially and operationally, IPM activities should be *programmed*. If an effective maintenance regime is in place, CM should play only a minor part in total maintenance activity; however, some unplanned "emergency" maintenance will always be needed and adequate resources need to be allocated for this purpose.

IPM is subdivided into the following categories:

a. *Planned replacement*: this ensures that building elements such as windows and roof finishes are replaced when they reach the end of their designated service life. Planned replacement minimizes the need for emergency maintenance and prevents the consequential damage which will occur if the element is left to fail.

b. *Preventive maintenance:* this ensures that building elements are well maintained and that they do indeed attain their designated service life. This can be achieved by *routine scheduled maintenance*, for example regular redecoration of windows or regular lubrication of mechanical components, or by *predictive maintenance*, i.e. dealing with a minor problem identified during a routine inspection, such as vibration in an air-conditioning unit, before it develops into a major problem and becomes an emergency.

Corrective maintenance, also known as emergency maintenance, is required whenever an unexpected problem arises which must be dealt with immediately. An effectively managed IPM programme will minimize the incidence of these events, but they can never be entirely avoided. There are two possible CM responses:

a. *Temporary repairs:* these aim to overcome the immediate problem and delay further consequential damage and loss – a temporary roof repair is one example. However, as soon as a temporary repair has been carried out, it is essential to schedule a permanent repair and to allocate funds for this work to be done promptly; otherwise the fault is likely to recur.

b. *Curative repairs:* these resolve the emergency in a permanent fashion. For example, if a cold-room refrigeration unit fails unexpectedly, it may be replaced with a new unit. Curative repairs should ensure a long period of trouble-free operation.

2.3 The building design and construction phase

The future maintenance requirements of a building are largely determined during the design and construction phases. The original client brief establishes the requirements that the design and construction teams should meet; a poorly drafted brief often leads to an inadequate building, so this is a vitally important

document. The subsequent building design together with the choice of materials and components and the way they are put together are also critical. If the maintenance implications of all these decisions are not considered – including the need for safe access for inspection, repair and replacement – there is a risk that long-term problems will be created and that these problems will recur throughout the life of the building. Finally, it is also essential that the standard of construction is properly monitored and that the contractor is prevented from substituting inferior materials or components to save money; this is something that frequently occurs, especially with design–build contracts. For all these reasons it is crucial that the maintenance team are consulted when the brief is being drafted, during the design process and throughout the construction phase.

All buildings used to store TTSPPs will be fitted with cold chain equipment – either cold stores or refrigerators and freezers. It is vital that this equipment is qualified before it is handed over for use. Readers should refer to the companion Technical Supplement: *Qualification of temperature-controlled storage areas* for details of this critical activity.

A fundamental prerequisite for effective maintenance is comprehensive and up-to-date information about the building and its installed equipment. For this reason, every building should have an operation and maintenance manual (O&M manual). In the case of a new building, this document is prepared by the contractor and contains the information needed for the day-to-day operation, maintenance, decommissioning and demolition of the building. In the case of an existing building for which no manual exists, as much as possible of the information listed in sections 2.3.1 and 2.3.2 should be collected and assembled by the organization(s) responsible for operating and maintaining the building. The O&M manual is essential, but ideally there should also be a separate health and safety file. These documents are described in the following sections.

2.3.1 The operation and maintenance manual[5]

In the case of a new or refurbished building the document should be prepared by the contractor with additional information from the designers (in particular the mechanical and electrical services engineer), material and component suppliers and the person responsible for operational health and safety issues – likely to be the Environmental, Health and Safety (EHS) Manager. The requirement to prepare the manual should be written into the building contract.

A draft version of the document should be provided for the client as part of the handover procedure before the building is accepted at the "practical completion" stage. The final document is not usually available in its full form until

[5] Sections 2.3.1 and 2.3.2 are adapted, with permission, from material at http://www.designingbuildings.co.uk relating to O&M manuals and health and safety files.

several months after practical completion because commissioning information often needs to include summer and winter or other seasonal readings taken in the fully occupied building. Both hard copy and electronic versions of the manual may be required and this should be clearly specified in the contract documents. For a large building the O&M manual will require multiple files and in all cases it is essential to assemble the material so that it is logically organized and easy to access. The elemental approach advocated in section 2.4.2 is one possible way to do this.

The O&M manual should include two main parts, namely, general operational guidance and detailed construction and operational information.

General operational guidance

This is an entirely separate, non-technical "building users' guide" or "building log book" with information for all users about how to use the building, covering energy efficiency, environmental controls, access, security and safety systems, and so forth.[6] This section requires particularly careful consideration because it will be widely used and needs to be easy to understand. In a warehouse used to store TTSPPs, the users' guide must also include all necessary information on the routine operation of the cold store(s) and other cold chain equipment.

Detailed construction and operational information:

This part contains:

- a description of the main design principles governing the site layout and building construction. In a phased project this description might usefully include a master plan and phasing programme for the site;
- details of the building's construction, covering the structural frame, service installations, cladding, doors and windows, roof construction, finishes, and so on;
- maintenance recommendations for individual systems, components and building elements. These recommendations should include manufacturers' instructions for correct and efficient operation as well as relevant health and safety information;
- as-built drawings and specifications;
- a register of plant and equipment installed in the building;
- commissioning and test results;

[6] See: Carbon Trust GPG348 Good practice guide: building log books – a user's guide (http://www.edocuments.co.uk/downloads/GPG348.pdf).

- guarantees, warranties and certificates of compliance;
- particular requirements for demolition, decommissioning and safe disposal of the building, its systems and components.

Much of this information will already exist in one form or another, so preparing the O&M manual should simply be a matter of compiling and assembling the relevant material.

Over the life of the buildings, the O&M manual should be updated to reflect changes to the fabric of the building and its systems, together with details of maintenance that has taken place.

2.3.2 The health and safety file

As noted above, the O&M manual should contain health and safety information relating to specific systems, components or building elements. However, the format of the O&M manual can make this information difficult to find and genuinely important safety issues may be overlooked. It is therefore good practice to have a separate health and safety file; this should include the specific information needed to enable cleaning, maintenance, refurbishment, alterations and eventual demolition to be carried out safely.

The contents of the health and safety file will vary depending on the nature of the works being carried out; however, it may contain:

- a description of the project;
- a description of any residual hazards that should be managed;
- the structural principles of the design;
- identification of any hazardous materials used;
- information about cleaning and maintenance equipment;
- information about safe working in cold stores;
- procedures for the safe removal or dismantling of installed plant and equipment;
- a description of significant services and their location;
- information and as-built drawings of the structure, plant and equipment.

The health and safety file must be kept up to date. It must be available for inspection by all interested parties so that any work to the building can be planned and carried out safely with full knowledge, and potential hazards can be managed.

The health and safety file is normally kept for the lifetime of the building; it should be passed on to the new owners if the building is sold, and the new owners should be informed of its purpose and importance.

2.4 Maintenance management

In the public health sector, one of the underlying reasons for inadequate maintenance is that the building and the site on which it is located may not be under the direct control of the ministry of health, but may be managed by a separate property services or public works department. Under these circumstances health sector managers may not have the authority or knowledge that is needed to implement an effective maintenance regime, even if they understand what actions need to be taken. At the same time, the property services or public works department may not understand, or be able to meet, the specific maintenance needs of a pharmaceutical warehouse, especially one equipped with complex refrigeration equipment.

A further challenge, especially in low- and middle-income countries, is that the annual budgeting process and competing demands for scarce resources make it difficult to fund and manage multi-year planned maintenance programmes of the type advocated in this document. Maintenance activities involve both capital and recurrent expenditure; some planned maintenance activities, such as servicing of mechanical plant, may fit into an annual funding cycle whereas others, such as redecoration or the replacement of roof finishes, carried out at infrequent intervals of years or decades, may not be regarded as a funding priority, and may be delayed until damage to the building and contents has occurred.

2.4.1 Establish an institutional or contractual framework

Ideally, maintenance management should be assigned to an existing facility management agency or department, staffed by professionally qualified facility managers. If such an organization does not exist, it is essential to establish an effective institutional framework to manage maintenance activities.

In situations where building maintenance is a direct programme responsibility, the responsible personnel should know how to inspect buildings, how to instruct and supervise basic building work, how to liaise with specialist contractors and how to plan and control a maintenance budget.

In all situations where responsibility for maintenance rests elsewhere in the government sector, a Memorandum of Understanding (MoU) should be drawn up with the responsible agency or department; this document should incorporate a service level agreement (SLA) stating the specific maintenance standards and emergency response times that are required in order to protect valuable pharmaceutical products from damage or loss. Similarly, in situations where maintenance activities are outsourced to a commercial operation, there must be a comprehensive contractual agreement and SLA which includes a clear statement of the responsibilities of the contracting parties, measurable key performance indicators, and financial penalties for non-compliance.

In all cases, roles and responsibilities should be clearly defined; responsible personnel should receive appropriate specialist training in pharmaceutical

warehouse maintenance and should know with whom to liaise in the relevant ministries, departments and external maintenance service providers.

2.4.2 Preventive maintenance and replacement: standards and schedules

It is important to establish objective evidence-based maintenance and replacement standards from the outset; this will enable maintenance personnel to make rational decisions during routine periodic inspections of the building and will provide managers with the evidence needed to advocate for funding and action.

As an extension to the O&M manual, the first step is to develop a systematic maintenance planning and costing system incorporating these standards. A standard coding structure should be used to identify and characterize the key parts of the building. A widely used classification system is Uniclass, which divides a building up into individual elements – see **Annex 1**.[7] Table 1 is a simplified list of these codes as they might apply to a steel-framed warehouse; the example ignores external works such as perimeter fencing and underground drainage.

Table 1
Coding system for a simple warehouse

G2 – Fabric	G21 – Foundations
	G22 – Floors
	G23 – Stairs
	G24 – Roofs
	G25 – Walls
	G26 – Frame
G4 – Fittings/furniture/ equipment (FFE)	G44 – Sanitary, hygiene FFE
	G45 – Cleaning, maintenance FFE
	G46 – Storage FFE (e.g. pallet racking)
G5 – Services	G50 – Water supply
	G51 – Gas supply
	G52 – Heating, ventilation and air conditioning (HVAC)
	G53 – Electric power
	G54 – Lighting
	G55 – Communications
	G57 – Protection (e.g. firefighting systems)
External decoration	
Internal decoration	

[7] See also: http://en.wikipedia.org/wiki/Uniclass

Each of these elements can be further subdivided as needed. Thus a roof assembly might be broken down into ceiling linings, thermal insulation and roof covering if these are separate components, or classified as a single element in the case of a factory-made composite panel. An inspection timetable, an evidence-based planned replacement schedule and a preventive maintenance standard can then be set for each element. This information can be recorded in an electronic database or in tabular form on paper. The database can then be used as a basis for maintenance planning and for drawing up IPM checklists. Table 2 shows an example of an entry for a composite panel roofing system. In this case, the replacement interval and the preventive maintenance actions are based on the hypothetical manufacturer's warranty and maintenance recommendations. Other elements may require the professional judgement of the facility or maintenance manager.

Since these records will accompany the building throughout its lifetime, it is important to list all changes made as they occur. For example, if the roof cladding is replaced by another product, the record needs to reflect this change because the maintenance schedule and appropriate actions may also change. Construction drawings and other technical information (if they exist) should also be referenced in the record so that the relevant as-built construction and product details held in the O&M manual can easily be accessed and checked when needed.

Finally, if an electronic database is used, the record could be extended to include details of work periodically instructed and carried out, together with payments made. With a paper-based system this information can be classified using the same coding system and filed separately.

Table 2
Example of an elemental maintenance record

Element inspection, replacement and maintenance task record	
Location	South Warehouse
Element	G24 – Roof
Sub-element	G24.1 – External cladding
Description	Supaclad TS100RW composite panels, 70 mm PIR insulation, through fixed
Relevant drawings	SW-L1003B, SW-D1050D
Technical information	O&M manual section G24.1
Replacement interval and rationale	25 years (25-year thermal performance warranty, 30-year coating warranty)

Table 2 *continued*

Element inspection, replacement and maintenance task record	
Inspection schedule	5 yearly, starting December 2008
Inspection tasks	• Check for leaks • Check for build-up of dirt and organic matter which can trap water and cause corrosion • Check for damage and corrosion to external and internal surfaces, especially at cut edges, laps and overhangs • Check fixings and fixing caps • Check sealant tape at laps
Safe access requirements	• Mobile access platform for internal lining inspection • Use fall arrest harness with access by fixed ladder at north end
Preventive maintenance actions	• Wash off organic build-up • Prepare and recoat damaged or corroded areas using Supaclad TS100RW repair kit • Replace loose or damaged through fixings and replace missing caps • Replace damaged or displaced joint sealant tape

Revision date	**Change summary**	**Reason for change**	**Approved**
10 Dec 2008	Original	Nil	AG
20 Dec 2013	Sealant tape check added	Omission corrected after first 5-year inspection	IM

2.4.3 Establish a multi-year maintenance plan

Once maintenance standards and schedules have been set for the various building elements, as described above, the next step is to develop a multi-year maintenance plan for the building. This plan should be updated once a year, should cover a rolling period of at least five years, and should include the following elements:

- *An itemized maintenance plan*, based upon a thorough inspection of the building and site. The plan should cover the following items: major renewal work that can be foreseen, such as re-roofing; periodic external redecoration; periodic internal redecoration; routine annual maintenance of mechanical equipment such as heating systems, air-

conditioning units, refrigeration units and ventilation fans; periodic maintenance of drainage systems, including cleaning of drainage ditches, septic tanks and the like.

- *A maintenance budget* based upon the requirements of the maintenance plan. It is essential that the budget is realistic, accurately reflects the anticipated costs for each item and takes account of anticipated inflation over the period covered by the plan. On the assumption that budgets are set annually, the first year's budget will form the basis for the annual funding application to the relevant ministry or other funding authority. The budget for the second and subsequent year's anticipated work should be submitted for information so that the funding authority is alerted to the need to set aside funds in these years.
- *A financial control and costing system* to ensure that funds are disbursed correctly. This process is highly context dependent and specific guidance on procedures cannot be given here.
- *A programme of work* that will achieve the targets set in the maintenance plan. Where maintenance activities are outsourced, the programme should reflect the bidding process and/or the process of contract negotiation when long-term service agreements are up for renewal.
- *An effective reporting system*.

Planned maintenance must then be carried out in accordance with the schedule to ensure that the building and site remain in good condition.

Arrangements must also be in place to ensure that emergency maintenance takes place promptly so that TTSPPs and other supplies are protected from damage – see section 2.4.6.

2.4.4 Planned periodic inspections

To ensure that maintenance problems are detected, systematic inspections of the building must be carried out. These should be conducted at regular planned intervals, using facility-specific and element-specific checklists. When preparing an inspection plan, consider the following:

a. *When should inspections take place?* Typically there should be a general annual inspection of the entire building. These inspections should be used to validate the timing of planned cyclical maintenance activities, such as redecoration, and should also be used to identify defects that require immediate attention and cannot

be left until their scheduled maintenance date. Other planned inspections may focus on specific elements and should take place at the intervals specified on the maintenance record sheets. For example, comprehensive inspection and testing of the electrical system might take place every 15 years. Finally, unscheduled emergency inspections should be carried out whenever the building users report a significant problem or failure.

b. *What should be inspected?* As noted above, the annual inspection will be a general inspection. Element-specific inspections may be grouped together by interval and the inspection procedure should follow the items listed in the element record. **Annex 2** gives an example of a checklist for the external envelope of a cold store.

c. *Who should carry out the inspection?* Many inspections will be conducted by the facility or maintenance manager or his or her nominated staff. However, some inspections need to be carried out by a qualified specialist or technician. The 15-yearly electrical system inspection referred to above is one example – in a smaller building this would be carried out by a qualified electrician; in a larger building with complex systems, by an electrical engineer. Another example of a specialist inspection is a planned service visit of the type described in section 2.4.5.

d. *When should elements be repaired?* There is an old saying that "a stitch in time saves nine". Cyclical repairs and redecorations, carried out at planned intervals, prevent degradation and extend service life and it is a false economy to extend these intervals. Similarly, emergency repairs should be carried out promptly in order to prevent further damage to the element itself and knock-on damage to other elements.

e. *When should elements and components be replaced?* Some building elements – for example structural frames and masonry external walls – are expected to last the lifetime of the building. Repairs, such as redecoration, repointing or re-rendering may be needed at intervals of years or decades but, generally speaking, any fundamental failure of these elements will indicate the end of the building's economic life.

Other building elements and components that are designed with periodic replacement in mind should be replaced at the point where the disruption caused by failure and the cost of emergency repairs makes this the best option. For initial planning purposes, the material or component manufacturer's estimate of service life can be used as a basis for budgeting. However, actual conditions of use, user

behaviour and the quality of routine preventive maintenance will affect the replacement date. Good maintenance, careful users and a benign climate will lengthen service life; poor maintenance, careless users and harsh climatic conditions will all shorten it. Accordingly, the replacement date should be kept under review and reassessed at the time of each planned inspection.

There may also be other reasons for replacement. For example, increases in energy costs might make it economically attractive to replace or over-clad a poorly insulated building envelope with a highly insulated product, even though the existing envelope is still in good condition. This would be an example of improvement – see Figure 2.

2.4.5 Planned service inspections

Service inspections are different from planned periodic inspections. Typically they apply to mechanical equipment, are carried out by a qualified technician, and involve specific maintenance actions such as lubrication, replacement of consumable parts such as filters and other time-dependent actions recommended by the equipment manufacturer. Such inspections may take place several times a year.

2.4.6 Curative maintenance

Curative (emergency) maintenance should be carried out as rapidly as possible, consistent with the identified risk. For example a failed refrigeration unit in a cold room with a duplicate refrigeration unit might reasonably be repaired within seven days because the duplicate unit can protect the stored TTSPPs in the meantime. However, if there is only one refrigeration unit, the risk of immediate product damage is acute; unless the product can be moved to another cold room, a 12–24 hour service response would be essential.

It is important therefore to carry out a risk assessment exercise to identify and classify critical maintenance emergencies and to establish a contingency plan to deal with them. Where time is of the essence, as in the example above, a maximum response period should be written into the relevant MoU or maintenance contract.

2.4.7 Organizing and managing the work

Maintenance can either be carried out using direct labour employed by the maintenance department, or it can be contracted out to an independent contractor. Table 3 and Table 4 show the opportunities and risks associated with

each option. The choice between the two approaches depends on the context and the type of maintenance work involved. For example, it might be appropriate to carry out general building maintenance using a direct labour team and contracting out the maintenance of specialist equipment such as standby generators, cold rooms and refrigerators to one or more specialist contractors. Under these circumstances, spare parts may be held by, or obtained through, the contractor or held by the government maintenance department and issued to the contractor as needed.

Table 3
Opportunities and risks for maintenance carried out by direct labour

Opportunities	Risks
Maintenance department controls workforce	• Controlling a workforce is time-consuming • Unless in-house planning is excellent, workers may be idle and workforce productivity will be low • Quality can only be maintained if the department has excellent supervisory skills
Workforce is on call and can be redeployed at short notice to deal with emergencies	• A full range of skills may not be available to deal with all tasks • If emergency call-outs are frequent, the workforce may be demotivated by unpredictable working patterns
A stable workforce will know and understand the buildings that they maintain	• Trained workers may leave for higher paid work in the private sector, leading to high staff turnover and poor skills retention
Bulk purchase of materials and spare parts can lead to financial savings	• The maintenance department has to operate supply depot(s) and manage a comprehensive inventory of tools, building materials and spare parts; this ties up capital • Infrequently required items may have to be bought in; this can lead to delays • Time-expiring materials, such as cement, may be wasted • Security can be a problem and materials and parts may be misappropriated

Table 4
Opportunities and risks for contracted out maintenance

Opportunities	Risks
Potential access to a wide range of outsourced maintenance service providers	• Poorly drafted outsourcing contracts and SLAs and/or poor contract management can lead to poor levels of service and contractual disputes • Service levels can be affected if the contractor prioritizes other clients • In lower income countries, some of the specialist skills required may not be available in the private sector
Risk and management responsibility is outsourced	• Cost control can be a problem unless the contract has tightly defined remuneration rates for specific tasks • Standards of work may be unsatisfactory unless rigorously monitored by the facility or maintenance manager
Poorly performing contractors can be delisted and replaced	• Contract termination is time-consuming and disruptive and may lead to disputes unless contract terms and conditions, performance indicators and penalties are tightly defined
Payment is only made on completion of the task (or on a retrospective interim basis for longer-term works)	• Payments to the contractor may be delayed unless the maintenance department is granted adequate working funds and authority to disburse them • Delayed payments can lead to contractual disputes, delays to the work and poor performance • Corrupt relationships with outsourced contractors are possible unless there is tight financial control and oversight

2.4.8 Inspecting and signing off the work

It is essential that the quality and completeness of all significant maintenance work should be inspected and signed off. Generally this function should be carried out by a supervisor attached to the management team. However, in some circumstances a specialist contractor may certify work as complete and satisfactory by providing the client with a signed copy of a completion and/or test certificate. This applies particularly to the servicing of mechanical and electrical

equipment and services, especially where the original equipment manufacturer publishes clearly defined service instructions. In countries with effective trade certification procedures, this form of self-certification is common practice; in the event of a dispute, the contractor's certifying body can be brought in to adjudicate. In countries without such schemes, self-certification is more risky and the quality of self-certified work should be independently checked.

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  - Guide 3: How to procure and commission your healthcare technology (http://www.healthpartners-int.co.uk/our_expertise/HCTGuide3.pdf).
  - Guide 4: How to operate your healthcare technology effectively and safely (http://www.healthpartners-int.co.uk/our_expertise/HCTGuide4.pdf).
  - Guide 5: How to organize the maintenance of your healthcare technology: management http://www.healthpartners-int.co.uk/our_expertise/HCTGuide5.pdf).
  - Guide 6: How to manage the finances of your healthcare technology management teams (http://www.healthpartners-int.co.uk/our_expertise/HCTGuide6.pdf).

Annex 1

Uniclass: building elements

Note: External and internal decoration have been added to the list; these essential global maintenance items do not appear in the Uniclass system.

G1 – Site preparation	G11 – Site clearance
	G12 – Ground contouring
	G13 – Stabilization
G2 – Fabric	G21 – Foundations
	G22 – Floors
	G23 – Stairs
	G24 – Roofs
	G25 – Walls
	G26 – Frame/isolated structural members
G3 – Fabric: parts of elements	G31 – Carcass/structure/fabric
	G32 – Openings
	G33 – Internal finishes
	G331 – Floor finishes
	G34 – Other parts of fabric elements
G4 – Fittings/furniture/ equipment (FFE)	G41 – Circulation FFE
	G42 – Rest, work FFE
	G43 – Culinary FFE
	G44 – Sanitary, hygiene FFE
	G45 – Cleaning, maintenance FFE
	G46 – Storage, screening FFE
	G47 – Works of art, soft furnishings
	G48 – Special activity FFE
	G49 – Other FFE

G5 – Services: complete elements	G50 – Water supply
	G51 – Gas supply
	G52 – Heating, ventilation and air-conditioning (HVAC)
	G53 – Electric power
	G54 – Lighting
	G55 – Communications
	G56 – Transport
	G57 – Protection
	G58 – Removal/disposal
	G59 – Other services elements
G6 – Services: parts of elements	G61 – Energy generation/storage/conversion
	G62 – Non-energy treatment/storage
	G63 – Distribution
	G64 – Terminals
	G65 – Package units
	G66 – Monitoring and control
	G69 – Other parts of services elements
G7 – External/site works	G71 – Surface treatment
	G72 – Enclosure/division
	G73 – Special purpose works
	G74 – Fittings/furniture/equipment
	G75 – Mains supply
	G76 – External distributed services
	G77 – Site/underground drainage
External decoration	
Internal decoration	

Annex 2

Checklist for building weatherproofing

An example checklist for inspecting and repairing metal roof cladding and gutters is given in Table A2.1. A similar checklist could be used for metal wall cladding. This particular list is adapted from one prepared by the International Association of Cold Store Contractors (European Division).

It is crucial that the external envelope of a warehouse building protects the interior of the building, including cold store enclosures. There should also be a regular inspection of the inside of the roof, including crawl spaces above insulated cold store enclosures to check for roof leaks or significant build-up of condensation through insufficient air movement. Regular inspection and effective remedial action will prevent damage occurring. See companion Technical Supplement: *Maintenance of refrigeration equipment*.

Water leaks are most likely to arise from weather damage to the cladding or from overflowing gutters as a result of blockage. Accordingly, such inspections are best carried out during the rainy season, during or just after heavy rain.

Items in the Table that are marked with an asterisk should be checked shortly after the building is completed and thereafter annually. Other items should be checked at the intervals recommended by the cladding manufacturer.

Table A2.1
Example checklist for inspecting and repairing metal roof cladding and gutters

Inspection checklist		
Location:	South Warehouse	
Element:	G24 – Roof	
Check for	**Reason**	**Action**
*Leaks	Leaks may cause serious damage and corrosion within the building and may saturate insulation within the cladding system	Identify source of leak and repair in accordance with cladding manufacturer's recommendations
*Blocked gutters, downpipes and drainage	Blockages may cause overflow into the building	Clean and wash out any blockage

Table A2.1 *continued*

Check for	Reason	Action
*Local damage	Breakthrough of protective paint coating could cause corrosion of steel substrate	Assess extent and type of damage Possible actions: • Touch-up affected area in accordance with manufacturer's instructions • Over-paint affected area in accordance with manufacturer's instructions • Replace damaged sheet using matching material supplied by the original manufacturer
*Drilling swarf, rivet stems and other fixing debris	These can rust and cause staining	Remove debris
Dirt retention in areas of cladding not washed naturally by rainwater e.g. overhangs	This affects the appearance of the building and could, if left, cause breakdown of the coating	Wash down in accordance with manufacturer's instructions
Mould growth	This rarely occurs but can arise in extreme conditions and may affect appearance	Wash down and treat in accordance with manufacturer's instructions
Condition of fasteners	Faulty or inappropriate fasteners can cause leakage, or rust staining on the surface of the cladding, or both	Replace faulty fasteners and any missing caps
Corrosion of cut edges	Corrosion of cut edges at sheet overlaps and at overhangs can, if neglected, spread up the sheet	Apply treatment recommended in manufacturer's instructions
Changes in condition of the coating	Changes should be noted	Seek manufacturer's advice

* Check this item shortly after the building is completed and thereafter annually.

Revision history

Date	Change summary	Reason for change	Approved

Supplement 6

Temperature and humidity monitoring systems for fixed storage areas

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

Annex 9: Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products

May 2015

Contents

Abbreviations

3PL	third-party logistics (provider)
30DTR	30-day temperature recorder
GAMP	good automated manufacturing practice
GMP	good manufacturing practice
GSP	good storage practice
IQ	installation qualification
IT	information technology
LAN	local area network
MKT	mean kinetic temperature
OQ	operational qualification
PDA	personal digital assistant
PDA	parenteral drug association
PQ	performance qualification
RFID	radio frequency identification device
SaaS	solution as a service
SMS	short message service
TCP/IP	Transmission Control Protocol (TCP) and Internet Protocol (IP)
SOP	standard operating procedure
TTSPP	time- and temperature-sensitive pharmaceutical product
URS	user requirements specification
USB	universal serial bus

Acknowledgements

The authors of this document are Jean Bedard, MBA , Infitrak Inc. and Ryan Sanders, Infitrak Inc.

Glossary

3PL: Third-party logistics provider – a firm that provides service to its customers of outsourced (or "third party") logistics services for part, or all of their supply chain management functions.

Component: Any major piece, part or assembly of the main equipment or sub-equipment that does not have its own power supply and could not operate as a stand-alone unit (e.g. valves and switches).

Electronic temperature monitoring and event logger system: System for recording and reporting air and/or product temperatures, with optional facilities for recording and reporting specific events such as door-opening or defrost cycles, and for issuing alarms. Such systems may be user-programmable and may also be remotely monitored via a satellite link.

Mapping: Documented measurement of the temperature and/or relative humidity distribution within a storage area, including identification of hot and cold spots.

Operational qualification (OQ): The process of obtaining and documenting evidence, under controlled conditions, that the premises, equipment and supporting systems operate in accordance with their design specifications.

Performance qualification (PQ): The process of obtaining and documenting evidence that the premises, equipment and supporting systems, as connected together, will consistently perform in accordance with the approved process method and specifications.

Pharmaceutical product: Any product intended for human use or veterinary product intended for administration to food producing animals, presented in its finished dosage form, that is subject to control by pharmaceutical legislation in either the exporting or the importing state and includes products for which a prescription is required, products which may be sold to patients without a prescription, biologicals and vaccines. Medical devices are not included.[1]

Qualification: Action of proving that any premises, equipment and supporting systems work correctly and actually lead to the expected results. The meaning of the word *validation* is sometimes extended to incorporate the concept of qualification.

Refrigeration equipment: The term "refrigeration" or "refrigeration equipment" means any equipment whose purpose is to lower air and product temperatures and/or to control relative humidity.

[1] Definition from WHO/QAS/08.252 Rev 1 Sept 2009. *Proposal for revision of WHO good distribution practices for pharmaceutical products – Draft for comments.*

Standard operating procedure (SOP): A set of instructions having the force of a directive, covering those features of operations that lend themselves to a definite or standardized procedure without loss of effectiveness. Standard operating policies and procedures can be effective catalysts to drive performance improvement and improve organizational results.

Storage temperature: The temperature range listed on the TTSPP label, and within the regulatory filings, for long-term storage.

Temperature-controlled: Includes any environment in which the temperature is actively or passively controlled at a level different from that of the surrounding environment within precise predefined limits.

Temperature excursion: An event in which a TTSPP is exposed to temperatures outside the range(s) prescribed for storage and/or transport. Temperature ranges for storage and transport may be the same or different; they are determined by the product manufacturer, based on stability data.

Time and temperature-sensitive pharmaceutical product (TTSPP): Any pharmaceutical good or product which, when not stored or transported within predefined environmental conditions and/or within predefined time limits, is degraded to the extent that it no longer performs as originally intended.

Validation: Documented testing performed under highly controlled conditions, demonstrating that processes, methods, and systems consistently produce results meeting predetermined acceptance criteria.[2]

[2] Parenteral Drug Association (PDA). Technical Report No. 39: Guidance for temperature controlled medicinal products: maintaining the quality of temperature-sensitive medicinal products through the transportation environment. Bethesda (MD): PDA; 2007.

1. Introduction

This technical supplement has been written to amplify the recommendations given in section 4.5.2 and 4.5.4 of WHO Technical Report Series No. 961, 2011, Annex 9: *Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products*.[3] It covers the selection, installation and initial commissioning of temperature and humidity monitoring systems in fixed storage locations. It does not cover the routine operation of these systems. Related topics are covered in the following Technical Supplements:

- *Checking the accuracy of temperature control and monitoring devices*
- *Qualification of temperature-controlled storage areas*
- *Temperature and humidity monitoring systems for transport operations*
- *Temperature mapping of storage areas.*

1.1 Requirements

The Model guidance document defines minimum standards for temperature and humidity monitoring and alarm systems and components, and for the operational management of these systems.

1.1.1 Temperature monitoring systems

Air temperature monitoring systems and devices should be installed in all temperature-controlled rooms, cold rooms, freezer rooms, refrigerators and freezers used to store TTSPPs. Electronic sensors should be accurate to ± 0.5 °C or better.[4] Sensors should be located in areas where the greatest variability in temperature is expected to occur within the qualified storage volume and they should be positioned so as to be minimally affected by transient events such as door opening.

1.1.2 Humidity monitoring systems

Humidity monitoring systems and devices should be used in temperature-controlled rooms that are used to store TTSPPs that require a humidity-controlled environment. Monitoring sensors should be accurate to ± 5% relative humidity (RH) and located to monitor worst-case humidity levels within the qualified

[3] http://apps.who.int/medicinedocs/documents/s18683en/s18683en.pdf

[4] Alcohol, bi-metal, gas or vapour pressure thermometers are also covered, but the focus of this Supplement is on electronic systems.

storage volume. They should be positioned so as to be minimally affected by transient events such as door opening.

1.1.3 Alarm systems

Temperature, and where necessary, humidity alarm systems should be linked to the monitoring system(s) with high and low alarm set points. There should be a visual alarm and preferably also an audible alarm, together with automatic telephone dial-up or short message service (SMS) text warnings to key personnel.

1.2 Objectives

The objective of this Technical Supplement is to provide guidance on how to protect TTSPPs from damage by the correct use of electronic temperature monitoring systems. It describes how to establish requirements and define specifications for these systems and how to assure traceability of the data that are generated.

1.3 Target readership

This document is relevant to wholesalers, warehouse operators, distributors, dispatchers and 3PLs who store TTSPPs. The specific target audience within these organizations includes those who have direct responsibility for quality management, for example, quality assurance (QA) managers and operations managers.

2. Guidance

The ability to demonstrate compliance with good storage practice (GSP) is a regulatory requirement in most countries. Effective temperature monitoring and associated record-keeping is a critical component of GSP in all areas, however small, where TTSPPs are stored. In addition, depending on the products being stored, it may be necessary to monitor and record other environmental parameters, such as RH. Finally, there are operational events which may also need to be logged and recorded because they can have a significant impact on environmental control – for example door opening in freezer rooms and cold rooms.

2.1 Associated materials and equipment

None

2.2 Related activities

To enable this guidance to be fully applied, the following steps also have to be completed:

a. Identify the storage areas and equipment which will be used for storing TTSPPs and their relevant temperature regimes – ambient, controlled ambient, refrigerated and frozen.
b. Map these storage areas and equipment and determine hot and cold points. For areas that can be affected by seasonal changes, mapping should cover both cold and hot seasons. See *Technical Supplement: Temperature mapping of storage areas*.
c. Qualify the storage areas and storage equipment (installation qualification (IQ), operational qualification (OQ) and performance qualification (PQ)). See Technical Supplement: *Qualification of temperature-controlled storage areas*.
d. Ensure that all storage areas and equipment comply with applicable regulations and guidelines on the storage of TTSPPs before these products are brought into the store.

2.3 Choosing a monitoring system

In this context, a monitoring system generally refers to an automated system that simultaneously and continuously records and documents one or more physical parameters (such as temperature and relative humidity) at one or more predefined points. A monitoring system is used to record and document the conditions in various storage areas while minimizing the need for manual

measuring and recording. Such a monitoring system is increasingly required in facilities storing TTSPPs. This section outlines the steps that need to be taken to choose a suitable system or systems.

2.3.1 Prepare a user requirements specification

The first step in the process of commissioning and installing a monitoring system is to draw up a user requirements specification (URS). This is a document setting out the relevant compliance requirements, and the operational, technical and business needs. It also outlines the intended implementation programme. The document should be drafted by a suitably qualified person and then reviewed, revised and finalized in collaboration with all key departments such as quality management, warehousing, transport operations, and information technology (IT). Once the URS has been drafted, the implementation programme must be carefully planned.

2.3.2 Select the basic system type

There are two fundamentally different design options for a centralized monitoring system. The first is a hosted system and the second is the solution as a service (SaaS) approach.

- *Hosted system:* The monitoring system is fully installed and hosted by the commissioning organization. The server and database are stored, managed and maintained by the organization, which is also responsible for maintaining the system and ensuring its qualification.

  For small-scale facilities with limited cold chain equipment, such as primary health-care facilities and small pharmacies, the most appropriate hosted system will often be a stand-alone device; typically a simple portable electronic recorder which can be directly read by the person responsible for the cold chain equipment.
- *SaaS:* The monitoring system hardware (sensors and readers) is installed at the organization's site, but the software, server and database are hosted by the system supplier. The data are collected, stored and managed by the supplier and the organization has access to the data through a secure web interface. Under this arrangement, the system supplier ensures the system maintenance and qualification.

Choosing between these options is a key decision, with long-term operational and financial implications.

2.3.3 Match the system to the needs

Monitoring systems should be carefully chosen to match the specific needs of the application; this could be a small pharmaceutical store, a single large-

scale warehouse, or an operation with multiple warehousing sites. In addition, the type of organization is relevant; for example whether it is a 3PL, a wholesaler or a distributor. Each combination of operator and operation will have different monitoring and reporting requirements. The following sections provide some examples.

Large pharmaceutical warehouses: Large pharmaceutical warehouses typically have a complex infrastructure with a mix of storage areas. These may include primary warehousing, mezzanine floors, vaults and cages, cold rooms, walk-in coolers and refrigerators and freezers. These organizations require reliable and adaptable monitoring systems with hardware that is designed for use on industrial sites. Wireless (radio frequency (RF)) sensor networks are a suitable technology for these types of facility. Alternatively, hard-wired sensor systems may be used. Regardless of the system chosen, it is essential that it is compatible with the storage environment and can be altered and extended as necessary to suit changing needs. A web-based system, centrally hosted and monitored by the organization, is typically used by these types of facility.

Hospitals: Pharmacies, laboratories, blood and tissue banks are typical of the hospital storage areas that need to be equipped with a monitoring system. These institutions have specific communication and technical requirements, and system compatibility challenges (e.g. wireless communication) that may limit system choice.

Small-scale pharmacies and laboratories: Pharmacies and laboratories may find it cheaper and more convenient to use an externally hosted SaaS system because of the cost and complexity of the IT and operational requirements needed to support an in-house hosted system. Hardware is installed in the storage areas but the supplier hosts the software and the database, making the data accessible on demand. This type of system generally uses wireless sensors (RF or WiFi), as they are easier to install in smaller facilities than wired systems. The size and location of the facility will determine the final choice; at the smaller end of the scale there is an overlap with small storage facilities.

Small storage facilities: These facilities also require reliable and adaptable monitoring systems. Small storage facilities typically have limited equipment for storing TTSPPs, such as a small walk-in cold room and/or refrigerator(s) and freezer(s). In stores with several pieces of equipment, a small-scale version of a system suitable for large pharmaceutical warehouses may be appropriate. In peripheral stores such as health facilities or retail pharmacies a 30-day temperature recorder (30DTR)[5] may be all that is needed – see Figure 1.

[5] Typically these devices have an operating life of two or three years, after which they need to be replaced.

An SMS-enabled device can offer out-of-hours assurance because staff can receive alarm alerts on their mobile phones. A USB-enabled device allows temperature records to be downloaded and these records can then be reported to supervisory staff.

Figure 1
R30-day temperature recorders

FridgeTag2™ with USB

LogTag® temperature recorder

2.3.4 Automated continuous monitoring

The monitoring system should preferably be automated and continuous. Installing a real-time or nearly real-time data recording system is clearly an advantage, except in the smallest facilities. Automated data monitoring provides reliability advantages compared to manual measurements, which rely on human intervention. Because data need to be recorded accurately and continuously, a cost-effective and efficient monitoring platform is also required.

Automated monitoring systems provide an array of analytical and reporting functions that can be accessed easily from any connected device (computer, phone, or personal digital assistant). Reports based on time, date, activity, input, event type or multiple criteria can then be generated. Data can also be compiled and analysed over longer periods so that trending and risk analysis exercises can be conducted.

2.3.5 Data collection: wireless versus wired data transmission

A typical monitoring system consists of a network of sensors which are linked together to form an integrated electronic temperature and event logger system. Data transmission through this network may be done through wireless communication modes (e.g. Bluetooth, Wi-Fi, RF 418/433 MHz, 900 MHz) or through a wired network (e.g. Ethernet). Both system options can be either

installed as a stand-alone system or as an SaaS. The advantage of using an SaaS solution is that the management of the system as well as upgrades and validation and qualification are outsourced. Figure 2 illustrates some typical arrangements.

Figure 2
Monitoring system options

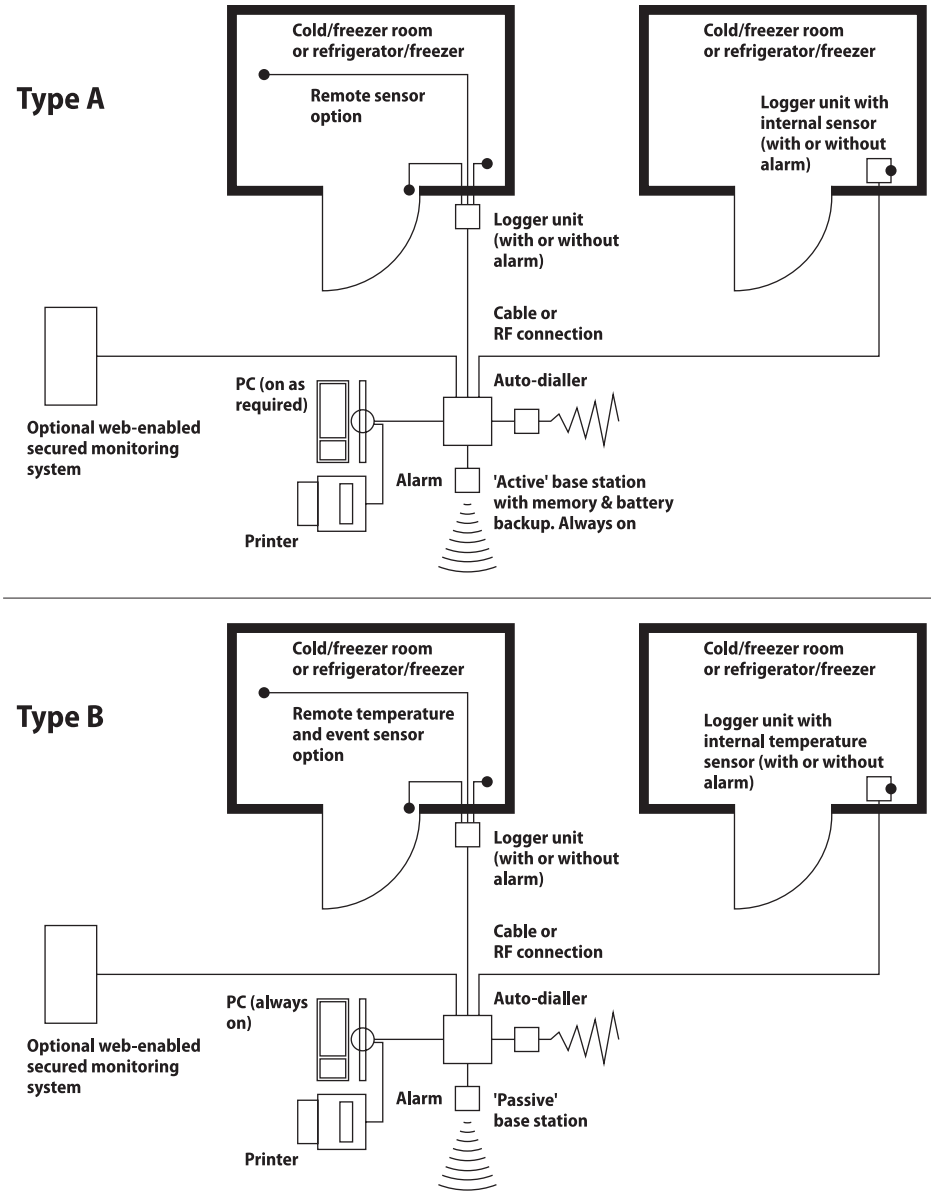
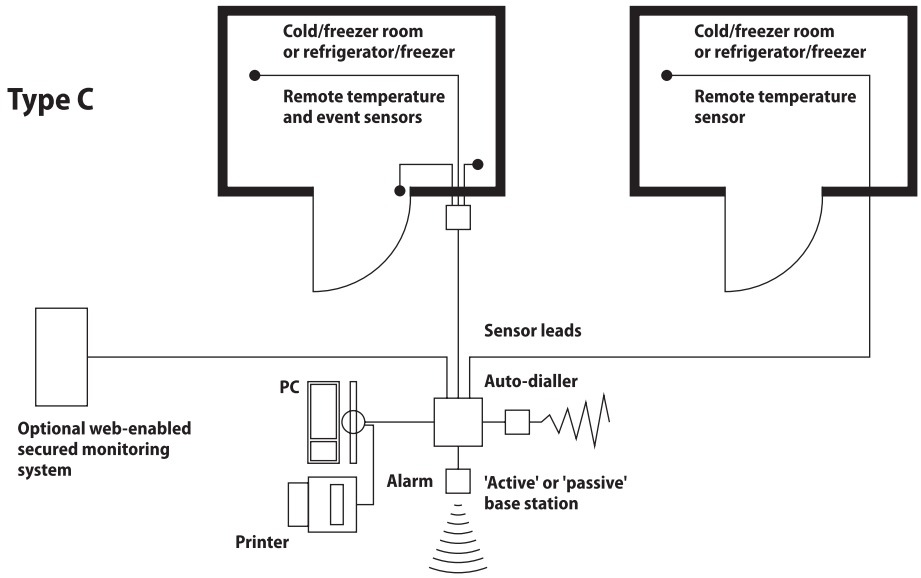


Figure 2 *continued*



Source: WHO/PQS

Wired sensors provide reliable data recording; however their installation can be complex and costly and this technology inhibits simple changes to the network configuration. Monitoring networks with wired sensors are also limited in terms of the adaptability of the monitoring architecture. This complicates matters when equipment needs to be moved, or a warehouse needs to be reconfigured, potentially incurring additional costs.

Wireless monitoring systems are now widely available, with different wireless transmission modes that can be adapted to suit the needs of the organization.

Wireless systems are supported on a local area network (LAN) and are easier to install and use; this reduces costs and the time required for installation and maintenance.

2.3.6 Specific requirements for wireless networks

Wireless sensor networks should have the following technical characteristics:

- Sensors should continuously collect and buffer data, even during network outages and power cuts. The buffered data should then be sent to the host server when the connection is re-established. Ideally, sensors should have a built-in data storage capability so that they can also act as data loggers.

- Sensors should be chosen to suit the different monitoring functions required in the network. This may include: temperature sensors for ambient and refrigerated stores, sensors with remote probes for low temperatures, temperature and RH sensors and sensors for logging events such as door opening.
- Sensor accuracy: ± 5% maximum accuracy. Generally speaking, a sensor accuracy of ± 0.5 °C or better should be expected.
- Sensors should be calibrated annually. An annual calibration plan for the system sensors should be drawn up and designed so that it can be carried out without major disruption to the monitoring process.
- The wireless sensor network should be self-adaptable, and self-healing: sensors should also act as data transmitters within the network.
- The wireless sensor network should automatically detect and incorporate newly installed sensors.

For a wireless system, the sensor-reader subsystem should also be evaluated in terms of transmission capability, efficacy (e.g. ability to transmit through walls or doors) and power consumption. In a complex or extended monitoring scenario, wireless configurations should be tested to avoid dead zones or wireless transmission concerns.

2.3.7 Web-based systems

Web-based systems should be user-friendly, even if they are required to perform complex operations. This minimizes training requirements, reduces the time taken to deploy the system and enables the user organization to obtain maximum performance.

Monitoring systems typically operate over existing LANs and wide area networks (WANs), using Transmission Control Protocol/Internet Protocol (TCP/IP), and should provide the ability to manage multiple users, buildings and sites.

Web-based systems generally emphasize ease of use, with system dashboards enabling the user to trace operations and activities, to see and follow up all alarms, and to compile data into preformatted reports. Web-based systems also allow the data to be stored in the Internet "cloud" rather than at a specific facility. Authorized users have access to an online database via secure access arrangements. When systems of this type are adopted they should be subject to system validation or qualification before use.

Monitoring solutions should incorporate a complete management system that includes the following features:

- user management;
- sensor inventory management;

- site calibration management;
- a system for reading the sensors, installed at every site;
- all sensors or tags clearly assigned to a specified location;
- management of alarm set points;
- a system for directing alarm messages to specific individuals;
- a system that allows rapid tracking of system activities; tracking could be by combinations of location, sensor, tag, document (e.g. waybill), user or date.

2.3.8 Alarm system

The monitoring system should include an integrated alarm function that reports out-of-range events. Alarms should be managed automatically. Alarm limits should be set only by authorized users and should automatically alert responsible staff by email, text (SMS) message or other communication medium in case of out-of-range events or incidents.

Available equipment includes combinations of audible and visual alarms and electronic messaging systems; the latter allow authorized users to be alerted via email, phone or text (SMS) message. A fully integrated system should allow the user to set an alarm schedule for different alert levels – for example workdays, weekends and holidays.

2.3.9 User controls

Data need to be recorded accurately and in real time, and should be provided in the form of reports, charts, and graphs, which users are able to customize.

The system should allow all sensor and alarm parameters to be configured and customized by users. For instance, it should be possible to configure the sensor recording (sampling) rate or set a variety of parameters for the alarm settings. These could include:

- low and high alarm threshold settings, triggered *before* temperature goes out of range;
- low and high alarm settings, triggered *after* temperature goes out of range;
- event alarms triggered by events such as mains power failure or door open.

Reports should be customizable by users allowing them to choose the format (text, pdf, graph), time period and content (high and low temperature events, mean kinetic temperature (MKT) analysis).

2.3.10 Adaptability and expandability

Unless the user requirement is very simple, it is wise to choose an adaptable and scalable system. A fully flexible system should support the following features:

- ease of configuration for small-scale or large-scale facilities;
- central monitoring of multiple remote sites;
- on-site hosting or vendor-hosting (SaaS);
- open architecture, allowing future expansion and upgradeability. Such systems can include enhanced features such as:
  - monitoring other parameters (e.g. airflow, pressure, flooding, movement),
  - integrated monitoring of transport systems (refrigerated and temperature-controlled vehicles or containers),[6]
  - automatically detecting and monitoring mobile sensors and tags (e.g. radio frequency identification device (RFID)).

It is important to determine both short-term and long-term needs. Making the correct initial choice makes it possible to scale appropriately if needed. Scaling possibilities can range from monitoring a specific storage area all the way up to installing a national cold chain monitoring system.

2.3.11 Security and compliance

Specific security and compliance requirements apply to monitoring systems and they should be installed and managed in accordance with relevant standards and regulations such as 21CFR part 11, and good automated manufacturing practice (GAMP). Specifically:

- Audit trails should be included in the system.
- The database and the data that it holds should be secured.
- There should be a comprehensive set of standard operating procedures (SOPs) covering installation, use, backup and decommissioning operations. For training purposes, a tutorial should also be available to users.
- Installed systems should be fully qualified by following the IQ, OQ and PQ sequence.
- The system should provide different "user levels"; each of these levels should have clearly defined authorization and access privileges.

[6] See Technical Supplement: *Temperature and humidity monitoring systems for transport operations*.

2.4 Maintenance and support

Monitoring systems are crucial to compliance with industry regulations and any system failures have to be resolved as rapidly as possible. Whether the system is hosted or SaaS, this means that a round the clock technical support plan should be part of the contract package. This package should include a requirement for the installer or service provider to cover maintenance, support and warranties for both hardware and software. The support period and the renewal arrangements need to be defined in the URS.

2.5 System extent

A comprehensive monitoring system for TTSPPs should be designed to record temperature and RH for all storage areas where these products are stored or temporarily held. The system should include the following areas:

- *General warehouse areas:* All warehousing areas, including distinct zones such as mezzanines and controlled ambient stores.
- *Cages, vaults and temporary holding areas:* Cages, vaults, preparation rooms and other spaces, such as packing, loading and quarantine areas where TTSPPs are handled and stored.
- *Cold chain equipment:* This includes equipment used to store TTSPPs in a refrigerated or frozen condition (freezer rooms, cold rooms, freezers and refrigerators).
- *Conditioning equipment:* Refrigerators and freezers used to store and condition cold chain packaging materials should ideally be linked into the monitoring system. These materials include ice-packs, cool water-packs, gel packs and phase change materials (PCMs).

2.5.1 Number of monitoring points

For ambient warehousing, controlled ambient stores, preparation rooms, temporary holding areas, freezer rooms, cold rooms and other spaces that people can physically enter, the number of monitoring points depends on the size of the space and on the diurnal and seasonal temperature variations observed during the mapping studies. This may differ from one facility to another. Refer to Technical Supplement: *Temperature mapping of storage areas*.

For small-scale reach-in equipment such as refrigerators and freezers, a minimum of one monitoring point or monitoring device should be installed in the storage chamber. *Note:* some national regulatory agencies require two sensors: one positioned at the coolest point and one positioned at the warmest point. The correct locations may be determined by on-site temperature mapping, or they may be determined during laboratory testing at the design qualification (DQ) stage.

2.5.2 Location of monitoring points

As previously noted, monitoring points should be located in all places where TTSPPs are stored or handled. The correct locations are established as follows:

- *Ambient and controlled ambient storage areas:* Position sensors in the places where seasonal hot and cold spots have been observed during the mapping studies.
- *Freezer rooms and cold rooms:* Position sensors in the places where operational hot and cold spots have been observed during the qualification and/or mapping studies.
- *Freezers and refrigerators:* See section 2.5.1.

Monitors should *not* be placed in areas where transient events such as a door opening may affect the monitoring and generate an abnormally high number of alarms. If such transient events generate out-of-range temperature alarms too frequently and the problem cannot be resolved technically or operationally (e.g. by limiting the number of door opening events), these areas should not be used to store TTSPPs and should not be monitored.

Note: Refer to Technical Supplement: *Temperature mapping of storage areas* for further information on how to determine hot and cold spots, based on the analysis of mean temperature.

2.6 Complementary services

Implementing an effective and reliable monitoring system is a complex task; its installation, operation and maintenance involve a number of complementary linked services. The scope of these complementary services needs to be clearly defined in terms of the answers the following questions:

- *Technical assistance and support:* What is the extent of the proposed technical service? What other technical assistance can the supplier provide? How will system problems (like component failure) be managed? Can spare components be kept at the site?
- *System maintenance and upgrades:* How will maintenance and system or component upgrades be managed? Is the system covered by a preventive maintenance programme?
- *Calibration:* How are sensors calibrated and by whom? How is calibration performed without disrupting the system?
- Regulatory compliance: What is the regulatory package provided with the system with regard to training, SOPs and qualification.

2.7 Deploying the system

Deployment is achieved by following a step-by-step process. The relevant departments in the commissioning organization (e.g. operations, IT, technical) must work closely with the system supplier to agree a deployment plan, and the execution of this plan must be closely monitored as the installation and commissioning activities proceed.

To streamline implementation, a *monitoring start-up form can* be used to facilitate an exchange between the organization and the supplier and cover all the points related to the system's deployment – see **Annex 1**.

2.8 Post-installation set-up and qualification activities

Once the system has been installed, the system operator will need to set the system parameters; this includes defining user privileges and alarm settings and so on. The system should then be operated for a commissioning period so that adjustments can be made and operational problems can be detected and resolved. Once the system is operating correctly it is time to perform final qualification (IQ/OQ/PQ) as described in the companion Technical Supplement: *Guidance on qualification practices for temperature-controlled storage areas*.

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Annex 1

Monitoring system start-up form example

SECTION 1: Person in charge

Contact details:
Name: Megapharm
Address: Unit 10, Erehwon Industrial Estate, Erehwon City
Tel.: +101 1234 5678
Fax: +101 1234 7891
Website/email: www.erehwon.com

Approvals:
Determine who will be responsible for the approval of the documentation.

Type						Name	Title	Department
Contract	User requirements	Specifications	Deployment	Qualification protocol	Change control			
✓				✓	✓		Project manager	Admin
	✓	✓		✓	✓		Quality assurance	QA
			✓				IT manager	IT

Employees in charge:
Determine who will be in charge of the different activities.

Project manager			
Name	**Title**	**Department**	**Phone/email**
Dr A. Projmann	Project Manager	Property Department	

SECTION 1: Person in charge

IT			
Name	**Title**	**Department**	**Phone/email**
Ms A. Hardrive	Systems Analyst	IT Department	
Quality assurance			
Name	**Title**	**Department**	**Phone/email**
Mr A. Qualman	Quality Manager	QA Department	
Instrumentation			
Name	**Title**	**Department**	**Phone/email**
Mr A. Instman	Quality Assistant	QA Department	
Maintenance			
Name	**Title**	**Department**	**Phone/email**
Ms A. Tidystore	Maintenance Manager	Property Department	
Security			
Name	**Title**	**Department**	**Phone/email**
Mr A. Guardian	Security Manager	Security Department	
Pager/Alarm			
Name	**Title**	**Department**	**Phone/email**
n/a			

SECTION 1: Person in charge

Miscellaneous

Name	Title	Department	Phone/email
n/a			

SECTION 2: Project description

Example:

- Installation of wireless sensors in South Warehouse (12 000 square metres), including one walk-in cooler and one walk-in freezer.

SECTION 3: Technological risk

Example:

- Very crowded storage area using many different types of radio frequency (RF) communication system.
- Energy source not always reliable.

SECTION 4: Regulatory risk

- None

SECTION 5: Data

- None

SECTION 6: Constraints

- Interference with the communication between wireless sensors and readers (antennas) may occur.

SECTION 7: Pre-installation checklist

☒ Availability of floor plan:
- South Warehouse plan SW-001B

☒ Location of Ethernet service panel:
- 3 locations in storage area plus server room SR01

☒ Availability of power outlet in Ethernet service panel:
- Same as above

☒ Availability of power outlet:
- See layout SW-001B

☐ Range of IP addresses:
-

☒ Location of server room (also on plan):
- See layout SW-001B, room SR01

☒ All equipment is clearly identified and listed.
-

☐ Location of antenna support panel ☒ Location of server room on plan

☒ Identification of potential causes of interference:
- Care needed in placing sensors and antennae. The warehouse is very crowded and there is much equipment that can interfere with the communication between wireless sensors and readers.

Required component summary

Comm/ power supply	**Qty**	**Temp. sensor**	**Qty**	**Humidity sensor**	**Qty**	**Wall plate/box**	**Qty**
Com manager	1	RF 900 MHz	28	RF 900 MHz	4	Wall mount	32
Power supply	1						

Comments
None

Revision history

Date	Change summary	Reason for change	Approved

Supplement 7

Qualification of temperature-controlled storage areas

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

Annex 9: Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products

May 2015

Contents

Abbreviations

CAPA	corrective and preventive action (procedures)
EDLM	electronic data logging monitor
IATA	International Air Transport Authority
IQ	installation qualification
OQ	operational qualification
PDA	Parenteral Drug Association
PQ	performance qualification
SMS	short message service
SOP	standard operating procedure
TTSPP	time- and temperature-sensitive pharmaceutical product
UPS	uninterrupted power supply

Acknowledgements

The author of this document is Jean Bedard MBA , Infitrak Inc.

Glossary

Auxiliary equipment: Equipment mostly used in conjunction with the equipment to be qualified but not included in the qualification package.

Component: Any major piece, part or assembly of the main equipment or sub-equipment that does not have its own power supply and could not operate as a stand-alone unit (e.g. valves and switches).

Controller, critical: A controller for which control has a direct impact on the quality of the product or proper operation of the equipment.

Controller, non-critical: A controller for which control has no direct impact on the quality of the product or proper operation of the equipment.

Controller: A device that interprets a mechanical, digital or analogue signal, generated by a sensor, to control an equipment or component.

Design qualification: The process of obtaining and documenting evidence that the premises, equipment and supporting systems and processes have been designed in accordance with the requirements for good manufacturing practices (GMP).[1]

Deviation: For installation qualification: any discrepancy between the installation specifications and the actual (as found) installation. For operational qualification: any discrepancy between the protocol and the actual performed test, test function methodology, testing equipment, and testing material.

Electronic data logging monitor (EDLM): A small portable device that measures and stores temperature readings at predetermined time intervals by means of an electronic sensor. These monitors have programmable alarm capabilities, integrated displays, and can create reports and graphs which may be permanently stored, shared and analysed via proprietary hardware, software, desktop application or through hosted databases.

Installation qualification (IQ): The process of obtaining and documenting evidence that the premises, equipment and supporting systems have been provided and installed in compliance with their design specifications.

Main equipment: Major equipment to be qualified.

Operational qualification (OQ): The process of obtaining and documenting evidence, under controlled conditions, that the premises, equipment and supporting systems operate in accordance with their design specifications.

[1] World Health Organization. WHO good manufacturing practices for pharmaceutical products: main principles. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-fifth report. Geneva: World Health Organization; 2011: Annex 3 (WHO Technical Report Series, No. 961).

Passive systems: Systems which maintain a temperature-controlled environment inside an insulated enclosure, with or without thermostatic regulation, using a finite amount of preconditioned coolant in the form of chilled or frozen gel packs, phase change materials, dry ice or others.

Performance qualification (PQ): The process of obtaining and documenting evidence that the premises, equipment and supporting systems, as connected together, will consistently perform in accordance with the approved process method and specifications.

Pharmaceutical product: Any product intended for human use or veterinary product intended for administration to food producing animals, presented in its finished dosage form, that is subject to control by pharmaceutical legislation in either the exporting or the importing state and includes products for which a prescription is required, products which may be sold to patients without a prescription, biologicals and vaccines. Medical devices are not included.[2]

Qualification: Action of proving that any premises, equipment and supporting systems work correctly and actually lead to the expected results. The meaning of the word *validation* is sometimes extended to incorporate the concept of qualification.

Qualified third party: An entity independent from the company that is mandated and involved in the preparation, execution or analysis of a quality assurance (QA) activity for the company. This third party should present the adequate professional qualification to perform QA activities.

Refrigeration equipment: The term “refrigeration” or “refrigeration equipment" means any equipment whose purpose is to lower air and product temperatures and/or to control relative humidity.

Sensor: A mechanical device (pressure switch, or bimetal temperature switch, a digital or analogue transducer (limit switch, pressure sensor, temperature sensor, etc.) that generates an electrical or mechanical signal to an instrument or a controller in order to be interpreted.

Spare parts: Parts that are available and may be used to replace or modify equipment components.

Standard operating procedure (SOP): A set of instructions having the force of a directive, covering those features of operations that lend themselves to

[2] Definition from WHO/QAS/08.252 Rev 1 Sept 2009. *Proposal for revision of WHO good distribution practices for pharmaceutical products – Draft for comments*.

a definite or standardized procedure without loss of effectiveness. Standard operating policies and procedures can be effective catalysts to drive performance improvement and improve organizational results.

Temperature excursion: An excursion event in which a TTSPP is exposed to temperatures outside the range(s) prescribed for storage and/or transport. Temperature ranges for storage and transport may be the same or different; they are determined by the product manufacturer, based on stability data.

Temperature-controlled: Includes any environment in which the temperature is actively or passively controlled at a level different from that of the surrounding environment within precise predefined limits.

Time and temperature-sensitive pharmaceutical product (TTSPP): Any pharmaceutical good or product which, when not stored or transported within predefined environmental conditions and/or within predefined time limits, is degraded to the extent that it no longer performs as originally intended.

Validation: Documented testing performed under highly controlled conditions, demonstrating that processes, methods, and systems consistently produce results meeting predetermined acceptance criteria.[3]

[3] Parenteral Drug Association (PDA). Technical Report No. 39: Guidance for temperature controlled medicinal products: Maintaining the quality of temperature-sensitive medicinal products through the transportation environment. Bethesda (MD): PDA; 2007.

1. Introduction

This Technical Supplement has been written to amplify the recommendations given in section 4.7 of WHO Technical Report Series No. 961, 2011, Annex 9: Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products.[4] It covers the three stages of qualification needed before the release of a temperature-controlled storage area for routine use: installation qualification (IQ), operational qualification (OQ) and performance qualification (PQ). Related topics are covered in the following Technical Supplements:

- *Checking the accuracy of temperature control and monitoring devices*
- *Qualification of shipping containers*
- *Qualification of temperature-controlled road vehicles*
- *Temperature and humidity monitoring systems for fixed storage areas*
- *Temperature mapping of storage areas.*

What is qualification?

In the context of this series of Technical Supplements, *qualification* is an inspection and testing process used to establish that a piece of equipment or a physical installation is fit for purpose in the operational context within which it will be used. There are typically three stages in the process. Each stage must be fully completed before the next one begins.

Stage 1 (for equipment): Establish by laboratory testing under tightly controlled conditions that a specific item of equipment performs in accordance with the user requirements specification (URS). This is *design qualification*. Although design qualification demonstrates compliance with the URS and associated test protocols, it does not prove that the equipment will be suitable in a specific operating environment because the URS and the test procedures are unlikely to reflect the full range of operating conditions.

Stage 1 (for installations): Establish by documented inspection and testing that an installation[5] that has been assembled in a specific location is fully in accordance with the URS and installation drawings. This is *installation qualification*.

[4] http://apps.who.int/medicinedocs/documents/s18683en/s18683en.pdf

[5] The installation will typically incorporate components that have a design qualification.

Stage 2: Establish by further documented testing under controlled conditions that this equipment or installation is likely to perform as intended in the operating environment in which it will be used. This is *operational qualification*.

Stage 3: Carry out a final stage of documented testing to establish with a high degree of assurance that the equipment or installation, together with all associated systems, does indeed perform as intended under routine operating conditions. This is *performance qualification*.

1.1 Requirements

Every new temperature-controlled store must be qualified before it is released for the routine storage of time- and temperature-sensitive pharmaceutical products (TTSPPs). As a minimum, the qualification procedure should:

- Establish that the installation, including all associated control, monitoring and alarm systems, has been carried out in accordance with the relevant drawings and specifications.
- Demonstrate, through temperature mapping, that air temperatures throughout the zone(s) designated for TTSPP storage are within the specified limits, both when empty and when in the normal loaded condition.
- Define zones which should not be used for storage of TTSPPs (for example areas in close proximity to cooling coils, cold air streams or heat sources).
- Demonstrate the time taken for temperatures to exceed the designated limits in the event of power failure, and the time taken to re-establish these limits following power restoration.
- Demonstrate the time taken for temperatures to return to within the designated limits following a representative door opening event.

Further qualification exercises should be conducted whenever significant modifications are made to the installation, or to the way in which it is used. The qualification process must be fully documented in order to demonstrate compliance to management, clients and regulatory authorities.

Qualification activities should be planned and documented. The plan should set out the sequence of testing activities to be carried out. It should also describe the method(s) for ensuring traceability between the individual test activities and the specific design features being tested.

1.2 Objectives

This Technical Supplement applies to fixed storage locations used for TTSPP logistic operations. The objective is to provide guidance on how to carry out the three types of qualification needed to meet the requirements of good storage practice in temperature-controlled areas. These are IQ, OQ and PQ.

1.3 Target readership

This document is relevant to wholesalers, warehouse operators, distributors, dispatchers and third-poarty logistics (3PLs) who store TTSPPs. The specific target audience within these organizations includes those who have direct responsibility for quality management, for example, quality assurance (QA) managers and operations managers.

2. Guidance

The purpose of qualification in the pharmaceutical and medical sector is to ensure that equipment or ancillary systems are properly installed, work correctly, and produce the specified performance outcomes under routine operating conditions.

2.1 Associated materials and equipment

A qualification operation requires a sufficient number of electronic data logging monitors (EDLMs) to ensure that qualification activities can be carried out correctly. In addition, suitable computer equipment and software is needed to store and analyse the data. The chosen EDLMs should:

- be technically suitable for the specific task and the intended operating environment;
- provide a continuous and reliable record of time-temperature data;
- have an appropriate temperature range so that all anticipated temperature extremes can be recorded (e.g. from −30.0 °C to +60.0 °C);
- have a user-programmable data sampling period allowing time intervals to be set in the range from 1 minute to 15 minutes or more and with sufficient memory for the intended length of the study and the chosen recording interval;
- have a NIST-traceable 3-point calibration certificate and have a guaranteed error of no more than ±0.5 °C at each calibration point;
- allow for recorded time-temperature data to be downloaded to a computer system for subsequent analysis;
- have data storage and analytical software that comply with applicable regulatory requirements (e.g. FDA 21 CFR part 11).

2.2 Introduction to qualification

Qualification is part of *validation*, but the individual qualification steps do not in themselves constitute process validation. Validation is the entire process by which a product is obtained from a manufacturer or distributor and is examined and tested before it is formally approved for routine use.

A qualification exercise generally consists of four sequential phases: design qualification (DQ), IQ, OQ, and PQ.

a. *DQ:* The purpose of DQ is to ensure that the premises, supporting utilities, equipment and processes have been designed in accordance with the relevant requirements (user requirements and regulatory requirements).

b. *IQ:* The purpose of IQ is to ensure that the premises, supporting utilities and equipment have been built and installed in compliance with their design specifications.

c. *OQ:* A successful OQ exercise provides assurance that the premises, supporting utilities and equipment operate in accordance with their design specifications. As a general rule, OQ is carried out on equipment when it is *empty*.

d. *PQ:* Following OQ, a PQ provides additional assurance through further testing that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes. The outcome of a successful PQ exercise is a formal confirmation that the equipment, associated systems and operational processes can be "released" for routine use. In contrast to OQ, PQ is carried out on equipment that is *loaded* with product.

2.2.1 Qualification applied to temperature-controlled storage

Qualification is commonly used to validate pharmaceutical manufacturing processes but it can also be applied to the pharmaceutical supply chain in general, and to temperature-controlled storage processes and equipment in particular.

In this context, temperature-controlled storage covers any area where TTSPPs have to be stored within a controlled temperature range (e.g. 2.0 °C to 8.0 °C or 15.0 °C to 25.0 °C). This includes:

- active temperature-controlled storage equipment, including ultra-low freezers, freezers, freezer rooms, refrigerators, cold rooms and controlled-ambient stores;
- actively temperature-controlled transport equipment. This includes refrigerated and temperature-controlled trucks and vans, and refrigerated and temperature-controlled ocean containers. Refer to the companion Technical Supplement: *Qualification of temperature-controlled road vehicles*;
- passive temperature-controlled packaging systems (shipping containers). This includes insulated containers used to maintain product temperature during road and air transport. Refer to the companion Technical Supplement: *Qualification of shipping containers*.

All temperature-controlled equipment and systems used to handle, store and distribute TTSPPs should be qualified.

An integrated IQ, OQ and PQ procedure is commonly used to qualify temperature-controlled storage areas. Ideally the IQ, OQ and PQ procedures

should be applied in a progressive and coordinated way, from the installation up to the final performance verification. However, this may be more difficult if the storage areas and equipment are already in use.

2.2.2 Installation qualification

The IQ process should be completed first. Its purpose is to ensure that the storage area and all its associated equipment and systems are clearly identified and have been correctly installed. This step must be completed before any further functional or operational tests are carried out.

Specifically, an IQ process should:

- Identify the storage area and the equipment and systems required for it to operate correctly and establish that all systems are installed as specified.
- Ensure that an effective preventive maintenance programme is in place.

2.2.3 Operational and performance qualification

Once the IQ stage has been completed, the OQ and PQ can generally be carried out together as a single sequence of inspections and tests. These inspections and tests should be chosen to suit the specific characteristics, performance needs and operational conditions of the storage area being qualified.

OQ is carried out with the storage area or equipment empty. It typically involves the following assessments:

- Verify applicable standard operating procedures (SOPs) or work instructions.
- Verify that all measuring devices (e.g. controllers and sensors) have valid calibration certificates.
- Carry out control panel tests and checks.
- Carry out alarm system tests and checks.
- Assess temperature control and temperature distribution in the empty storage space or equipment.[6]
- Check temperature recovery following a door opening.
- Conduct power failure tests and checks.

[6] See Technical Supplement: *Temperature mapping of storage areas*.

Note: In this context "empty storage space or equipment" means that no products are being stored and normal operations have yet to begin.

PQ is carried out with the storage area or equipment fully operational, loaded and having been allowed to reach stabilized conditions. The following tests and checks should be carried out:

- temperature control and temperature distribution;
- temperature recovery following a door opening.

Note: In this context "loaded storage space or equipment" means that the store or equipment has begun to receive products and normal operations have commenced.

2.3 Qualification protocols

Prepare, review and approve a detailed and comprehensive protocol before the qualification process begins.

The qualification protocol should be a comprehensive document, which guides the user through the IQ, OQ and PQ processes and helps ensure that all temperature-controlled storage areas are correctly qualified. Each of the three protocols can be more or less generic. However generic documents should never be used unthinkingly; they should always be adapted to the specific type of temperature-controlled storage area. Each installation must be linked to and qualified against its own specific qualification protocol.

The qualification protocol should include the following sections:

a. Approval page and change control history
b. Acronyms and glossary
c. Description and rationale
d. Scope and objectives
e. Key parameters
f. Procedures
g. Qualification report template.

2.3.1 Approval page and change control history

Include a standard template for recording approvals and changes to the document. Table 1 shows an example.

Table 1
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			

If the protocol has been prepared by a qualified third party, it should be authorized by the responsible person within the commissioning organization.

2.3.2 Acronyms and glossary

Define the acronyms and technical terms used in the protocol.

2.3.3 Description and rationale

Describe the installation to be qualified and the equipment and related systems to be included in the qualification exercise and outline the reasons for carrying out the exercise.

2.3.4 Scope and objectives

Clearly define the scope and objectives of the qualification exercise.

2.3.5 Key parameters

Describe the key parameters for the operation of the installation.

2.3.6 Procedures

The protocol for a specific installation should describe the procedure for every relevant test or check in detail, as follows:

a. *Title:* Briefly describe the test or check.
b. *Target:* Name the target system, subsystem or component.
c. *Procedure:* Clearly describe the test or check procedure as a step-by-step process. Specify any associated materials or test equipment required.
d. *Acceptance:* Define the acceptance criteria.
e. *Data collection:* Include templates for all the data collection and test sheets required.

A generic set of IQ, OQ and PQ tests and checks is outlined in sections 2.4 to 2.7.

2.3.7 Qualification report template

The protocol may contain a template for the qualification report. This should include everything needed to comply with internal rules and regulatory requirements, as follows:

a. *Introduction:* Describe the objectives of the qualification exercise.
b. *Summary:* Outline the results of the qualification exercise. Include a summary of all recorded deviations.
c. *Conclusions and recommendations:* State whether the installation can be used for routine operations. List all key recommendations that need to be acted upon; this should include a complete list of all changes that need to be made to the installation to correct reported failures recorded on the qualification inspection and test data sheets.
d. *Report annexes:* Append the following supporting material:
   - raw data as recorded on the appropriate inspection and test data sheets (see below) as well as all associated spreadsheets and graphs;
   - key documents and notes prepared during the qualification exercise, together with any other supporting material;
   - deviation reports, including corrective and preventive actions (CAPA) forms, if required;
   - calibration certificates for all EDLMs used;

- calibration certificates for the control and monitoring systems that form part of the installation;
- list of all members of the qualification team, and their designations.

All data sheets, results, spreadsheets and graphs must be reviewed by an independent person who was not involved in conducting the qualification exercise. The reviewer should confirm, approve and sign the results of the major tests and checks.

2.3.8 Approval process

If qualification is carried out as an in-house process, the IQ, OQ and PQ protocols and subsequent qualification reports must be authorized by the responsible manager(s) and quality assurance personnel within the organization.

If qualification is carried out by a qualified third party, both the IQ, OQ and PQ protocols and the subsequent qualification reports must be approved by the responsible person in the third-party organization.

2.4 Installation qualification

The purpose of IQ is to establish that all elements of the storage area, including building work, equipment, systems, subsystems and components are in accordance with the installation drawings and specifications. The first stage in the process is to itemize all these key elements. The next stage is to establish how each element should be inspected and tested to confirm compliance.

Once these preliminary stages have been completed, on-site inspection and testing can begin. The steps in the procedure are as follows:

- Carry out a detailed inspection of the storage area and all associated building works.
- Carry out a detailed inspection of the electrical services.
- Carry out a detailed inspection of the mechanical services.
- Carry out tests to confirm that the requirements for specified environmental conditions have been met.
- Identify, list and inspect the spare parts supplied as part of the installation.
- Identify, list and inspect any auxiliary equipment associated with, but not part of, the installation such as standby generators, security systems and the like.
- Confirm that satisfactory arrangements are in place to ensure an effective preventive maintenance programme for the entire installaton.

2.4.1 Identifying critical components

Although all parts of a temperature-controlled installation should be included in the IQ, there are certain critical elements that merit particularly close attention.

Refrigerators, freezers and other simple equipment: The critical parts of this type of equipment are the thermostat and its associated control sensor and the temperature monitoring device (thermometer or recorder) and its sensor; this may be a separate component such as a disposable 30-day temperature recorder.[7]

Complex equipment: This includes freezer rooms, cold rooms, pick coolers and more complex and specialized refrigerators and freezers, with a longer list of key components. Critical parts include the controller, sensor, cooling unit, condenser and evaporator. For freezer rooms and cold rooms, the room enclosure itself is also critical because these are sites assembled from separate panel elements.[8] All of these key components should be identified, listed, described and checked.

If the equipment has duplicates or multiples of any components or systems, each one should be checked. Critical components and systems that are directly involved in temperature control and measurement should also be checked for accuracy and calibration. Calibration certificates should be checked and copies included in the IQ report.

2.4.2 Checking installed systems, subsystems and components

Table 2 shows the type of record used to check and record installed systems and components. The example given here is for a cold room refrigeration unit.

Table 2
Example of an IQ inspection and test table

Subsystem or component inspection and test table	
Location:	South Warehouse
System:	Cold room #1
Subsystem/component:	Refrigeration unit #1
Inspection or test:	Inspection: ☒ Test: ☐
Type of inspection/test:	IQ protocol: visual check RFU-01

[7] See Technical Supplement: *Temperature and humidity monitoring systems for storage areas*.

[8] See Technical Supplement: *Refrigeration equipment maintenance* for a list of cold room enclosure checks.

Table 2 *continued*

Subsystem or component inspection and test table			
Details:	**Specified**	**As found**	**Pass or fail**
Manufacturer:	ABC refrigeration	ABC refrigeration	Pass
Model:	TTW50	TTW40	Fail
Serial number:	Not specified	TTW40-1310-025	Fail
Internal ID number:	CR1/RFU01	CR1/RFU01	Pass
Deviation report ref: Enter "none" if no deviation	DEV/001		
Inspected by:	AG	Date:	27 Oct 2013
Checked by:	JB	Date:	5 Nov 2013

For each system, subsystem or component, the table allows the IQ inspector to list the critical attributes of what was originally specified in the requirements specification or on the installation drawings (the "specified" column), what was actually installed (the "as found" column) and whether or not it complies (the "pass or fail" column).

a. *Specified conditions:* The entries for location, system, component and those in the "specified" column should be completed before the inspection begins. The same applies to the corresponding cells in Tables 3 and 4. Pre-filling in the table helps the IQ inspector to locate the listed item and check that it has been installed correctly. Where details are not available – in the above example the serial number of the refrigeration unit – enter "not specified". In addition, record whether an inspection and/or test(s) are to be carried out to assess compliance and describe the type of inspection and/or test(s) to be used. Key this back to the relevant section of the qualification protocol.

b. *As found column:* Use this column to record details of the item as found at the time of the inspection. To achieve a pass, the installed subsystem or component must meet or exceed the specified condition. In the example given in Table 2, although the refrigeration unit has been supplied by the specified manufacturer, the unit installed has a lower power rating than the one specified.

c. *Pass or fail column:* Compliance is achieved when an item fully meets or exceeds the specification or the specified performance conditions.

In the example in Table 2, the correct manufacturer has supplied the unit, so this is recorded as a pass. However, the refrigeration capacity of the installed unit is too small, so this is recorded as a fail.

d. *Deviation report:* Wherever a deviation is observed, this must be recorded on a separate deviation report form. Each inspection table should include a space to record a cross-reference to the relevant deviation report. If there are no deviations, enter "none". (For an example of a deviation report, see **Annex 1**.)
e. *Signatures:* The completed sheet should be signed or initialled by the inspector and checked by the designated reviewer.

Use drawings, photographs and other supporting material to expand and support the information recorded in the table.

2.4.3 Checking electrical systems and requirements

Because the installed electrical system typically connects to multiple components, it requires a separate inspection and qualification procedure. Table 3 can be used to record the overall compliance of the installed electrical system. Table 4 is used to identify and check the critical components of the system.

Table 3
Overall compliance check for electrical installation

Electrical installation: system compliance check sheet			
Location:	South Warehouse		
System:	Electrical installation		
Subsystem/component:	3-phase supply to cold room #1		
Inspection or test:	Inspection: ☒ Test: ☐		
Type of inspection/test:	IQ protocol: visual check ELEC-01		
Items	**Specified**	**As found**	**Pass or fail**
Main voltage (V):	415 V	415 V	Pass
Cycles (Hz):	50 Hz	50 Hz	Pass
Amperage (A):	100 A	100 A	Pass
Phase:	3	3	Pass
Inspected by:	*AG*	**Date:**	*27 Oct 2013*
Checked by:	JB	**Date:**	5 Nov 2013

Once the overall compliance check has been completed, the electrical supply to the individual critical components needs to be checked. The example below relates to the example in Table 2.

Table 4
Electrical installation: critical component checks

Electrical installation: critical component check sheet				
Location:	South Warehouse			
System:	Electrical installation			
Subsystem/component:	3-phase supply to refrigeration unit A			
Inspection or test:	Inspection: ☒ Test: ☐			
Type of inspection/test:	IQ protocol: visual check ELEC-05			
Electric supply	**Specified**	**As found**		**Pass or fail**
Breaker location/service panel	Panel A	Panel A		Pass
Circuit/breaker number	Not specified	RFU-1		Pass
Circuit voltage (V)	315	315		Pass
Circuit amperage (A)	30 A	20 A		Fail
Circuit phase	3	3		Pass
Emergency power?	Required	Yes ☒	No ☐	Pass
Isolating switch?	Required	Yes ☒	No ☐	Pass
Is the electrical supply compatible with electrical requirement?	Required	Yes ☐	No ☒	Fail
Grounded?	Required	Yes ☒	No ☐	Pass
Special isolation/ shielding?	Not required	Yes ☐	No ☒	Pass
Is the circuit-breaker properly identified?	Required	Yes ☒	No ☐	Pass
Inspected by:	*AG*	**Date:**		*27 Oct 2013*
Checked by:	JB	**Date:**		5 Nov 2013

The service panel and circuit-breakers that apply to the various critical components should be clearly labelled both at the service panel itself and at the component.

2.4.4 Checking environmental conditions

Check the environmental conditions in the storage area and check all installed equipment and components for cleanliness, fumes, and vibrations. Record the temperature and relative humidity conditions and determine whether these are within the limits designated in the IQ protocol (Table 5).

Table 5
Environmental conditions, control and monitoring checks

Environmental control and monitoring system check sheet			
Location:	South Warehouse		
System:	Cold room #1		
Subsystem/component:	As above		
Inspection or test:	Inspection: ☒ Test: ☐		
Type of inspection/test:	IQ protocol: visual check ENV-01 and instrumented measurement ENV-02		
Items	**Specified**	**As found**	**Pass or fail**
Cleanliness:	All surfaces clean	Floor dusty	Fail
Fumes:	None perceptible	None perceptible	Pass
Vibrations:	None perceptible	RFU #1 vibrating	Fail
Temperature control:	Single sensor	Single sensor	Pass
Humidity control:	No active control	No active control	Pass
Temperature monitoring:	3 sensors	3 sensors	Pass
Humidity monitoring:	None	None	Pass
Temperature (°C):	+2.0 °C to +8.0 °C	+5.5 °C (sensor 1) +6.1 °C (sensor 2) +4.9 °C (sensor 3)	Pass
Humidity (% RH):	60% to 75%	70%	Pass
Inspected by:	*AG*	**Date:**	*27 Oct 2013*
Checked by:	JB	**Date:**	5 Nov 2013

2.4.5 Checking spare parts

If applicable, include a section in the IQ report on change parts and list those that have been provided as part of the installation. These parts need to be checked for compliance as described above in section 2.4.1.

2.4.6 Checking auxiliary equipment

The installation may have auxiliary equipment associated with it, which is not directly included in the scope of the IQ inspection. An example might be a security and alarm system. This equipment should be identified and listed in the IQ report. The report should also include a description of the electrical, electronic or other interfaces between this equipment and the installation itself.

2.4.7 Checking information needed for the preventive maintenance programme

An effective preventive maintenance programme (PMP) cannot be implemented unless the relevant key elements are in place. The IQ inspector should check the following:

a. Are all the items of equipment and all key components listed in the equipment inventory?
b. Are all these items labelled in accordance with the organization's equipment management policies?
c. Is there an equipment inventory file, and where is it located?
d. Is there a maintenance logbook, and where is it located?

All relevant documentation, drawings and installation and commissioning records should be collected together in an equipment file and attached to the IQ report. Table 6 shows one way to index this information in tabular form.

Table 6
Equipment file index

Information available in the equipment file							
Equipment or component ID	Equipment or component name	TS	OI	MI	RS	Record type	Record number

TS, technical specifications; OI, operating instructions; MI, maintenance instructions; RS, recommended spare parts list.

2.4.8 Writing the IQ report

As soon as the IQ assessment has been completed, prepare a report as outlined above in section 2.3.1 Pay particular attention to the following points:

- Make sure that all of the sections included in the IQ protocol have been completed, signed and dated.
- Record all deviations from the installation drawings and specifications in the deviation report section. Make sure that each deviation is cross-referenced to the relevant sections of the IQ protocol.
- Specify the actions that need to be taken to correct the reported deviations and state the name of the person or organization responsible for completing these actions.
- Merge any handwritten logbook notes made by the IQ team into the relevant sections of the report.
- List all members of the qualification team, and their designations.

2.5 Operational qualification

Do not begin the OQ stage until all relevant deviations recorded during the IQ inspection have been corrected.

The purpose of OQ is to establish that the installation and all its systems and subsystems operate effectively and consistently when the storage area is *empty*. As soon as the OQ process has been completed and the installation has been approved, the next step is the PQ stage, with the storage area *fully operational*. Once the entire OQ and PQ process has been successfully completed, the installation can be signed off and fully released for routine operation.

An OQ inspection should cover the following:

- Check the calibration of all temperature measuring and controlling systems and components.
- Test the installation's control systems and check that these systems function correctly. Check the system set points.
- If there is a temperature alarm system, set the low and high alarm limits and set-up and test the relevant alarm outputs such as email messages, short message service (SMS) text messages and telephone contacts. Record the results.
- Carry out a temperature mapping of the empty storage area and record the results. See Technical Supplement: *Temperature mapping of storage areas*.

- Ensure that all relevant SOPs are available, that the relevant personnel have been trained to follow these SOPs and that training records are kept.

2.5.1 Checking installed systems, subsystems and components

As with the IQ procedure described in section 2.4.2, the OQ inspection and test tables and report should record the specified condition and the as found conditions and whether the as found condition is a pass or a fail. All deviations should be recorded, and the assessment results should be signed by the inspector and checked by the independent reviewer.

2.5.2 Calibration of controllers and sensors

All the controllers and sensors that form part of the installation should operate correctly and have valid calibration certificates. These certificates should be attached to the OQ report. Controllers and sensors should be suitably tagged so that they can be identified. Each tag should record the component ID, the calibration date and the calibration expiry date.

The objectives of the inspection are to:

- Check that all critical controllers and sensors have been calibrated and that the calibration status is current.
- Ensure that all these controllers and sensors are added to a calibration and preventive maintenance programme.

In order to meet the acceptance criteria, every critical controller and sensor should have:

- a current calibration certificate, with the certificate available;
- a calibration that is traceable to national standards;
- an attached calibration tag;
- an individual record in the calibration section of the preventive maintenance programme.

2.5.3 Standard operating procedures

There should be a comprehensive set of SOPs which cover all relevant aspects of the installation, routine operation and maintenance of the installation. These should be reviewed as follows:

- Check that that all the requisite SOPs have been written.
- Check that their content relates to the actual installed equipment and the specific operational requirements of the installation.
- Check that a training programme is in place, based on the content of the SOPs.

The following acceptance criteria apply:

- All SOPs must be approved and available.
- All SOPs must be consistent with operational requirements.
- There must be a training record, directly associated with each SOP, to demonstrate that training has been provided.

2.5.4 Control panel

The objective of the control panel inspection is to establish that all temperature controls, indicators and other displays operate in accordance with the manufacturer's specifications. This inspection is equipment-specific and should be drawn up to suit the system that has been installed.

The acceptance criterion is that all these elements are fully operational.

2.5.5 Alarm tests

The purpose of the alarm tests is to confirm that the alarm system operates in accordance with the design specifications. For temperature alarm systems, there should be one high alarm test and one low alarm test. If the system also has an event alarm system – for example a door open alarm – this should also be tested.

For each test, record the alarm settings and trigger the desired alarm event. Confirm that the alarm system is activated. Activation may be indicated by an alarm sounder or alarm strobe, by a signal to an alarm company, which provides a remote monitoring service (solution as a service (SaaS), by SMS or telephone message or by any combination of these options – all relevant systems need to be tested.

Once the alarm tests have been completed, record the results on an alarm system test sheet. A simple example is shown in Table 7. More complex alarm systems will need a more complex test sheet.

Table 7
Alarm system test sheet

Alarm system test sheet						
Test	**Operation**	**Compliance**		**Deviation report number**	**Tested by**	**Date**
		Yes	**No**			
High temperature alarm	Alarm activated	☐	☐			
Low temperature alarm	Alarm activated	☐	☐			
High alarm setting:						
Low alarm setting:						
Checked by:		Date:				

2.5.6 Temperature mapping – empty

The objective of the temperature mapping test is to demonstrate that the installation is capable of controlling and maintaining a uniform temperature when the storage area is empty. The whole area should be monitored for a period of at least 24 hours using EDLMs. Table 8 shows how the data should be recorded for an OQ test.

Table 8
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:**			

Note: The mapping procedure is fully described in the companion Technical Supplement: Temperature mapping of storage areas. Table 8 is taken from Annex 1 of that supplement.[9]

[9] The temperature mapping supplement recommends that mapping should be carried out in both the hottest and coldest months. However, for the purpose of OQ, only one mapping exercise is required.

2.5.7 Power failure test

The power failure test relies on the same data logger set-up as the temperature mapping test. The objective of the test sequence is to establish and record:

- The length of time during which the installation can maintain the specified temperature range following a power failure – this is known as the *holdover* time.
- How long it takes the installation to recover within the specified range once power is restored.

The results of these tests are simply recorded – there is no deviation report. For cold rooms, freezer rooms and other large temperature-controlled stores[10] there are usually no set acceptance criteria to be met in this test. However, the test data are useful to the store operator for emergency planning and other purposes; for example, planning the installation and operation of standby generators.

Power failure test:

a. *Power Failure up to Temperature Excursion:* To do the Power Failure verification, the storage area and equipment is powered off, and the temperature inside the storage area is recorded continuously. When the temperature inside the storage area goes out of range, then the storage area and equipment can be powered back on, and the time period to recover within the specified temperature range is determined;
b. *Fixed power failure period:* In this version of the test the power is stopped for a predefined period – for example, two hours – regardless of whether or not the temperature inside the storage area exceeds the required temperature range. Power is then returned and the time taken for the storage area to recover within the specified temperature range is measured.

Because both these tests may trigger a temperature excursion, carrying them out when the store is full of TTSPPs can place stored products at risk. For this reason it is best carried out during OQ when the store is empty. Table 9 gives an example of a power failure test sheet.

[10] In settings with unreliable electricity supplies, holdover is an important performance feature of mains-powered freezers and refrigerators. For WHO prequalified vaccine refrigerators, the holdover time is laboratory tested and reported. See the WHO PQS website at: http://apps.who.int/immunization_standards/vaccine_quality/pqs_catalogue/

Table 9
Power failure test sheet

Data logger ID number	Power off Time temperature was within range (hh:mm)	Power on Time to recover to within range (hh:mm)	Inspected by	Date
DL-001				
DL-002				
DL-003				
DL-004				
DL-005				
DL-006				
DL-007				
DL-008				
DL-009				
DL-XXX				
Power turned off at (hh:mm):				
Power turned on at (hh:mm):				
Checked by:		**Date:**		

2.5.8 Writing the OQ report

As soon as the OQ assessment has been completed, prepare a report as outlined above in section 2.3.1. Pay particular attention to the following points:

- Make sure that all of the sections included in the OQ protocol have been completed, signed and dated.
- Record all deviations from the installation drawings and specifications in the deviation report section. Make sure that each deviation is cross-referenced to the relevant sections of the OQ protocol.
- Transcribe any handwritten notes made by the OQ team into the relevant sections of the report.

- Specify the actions that need to be taken to correct the reported deviations and state the name of the person or organization responsible for completing these actions.
- List all members of the qualification team, and their designations.

2.6 Performance qualification

Do not begin the PQ stage until all of the deviations recorded during the OQ inspection have been corrected.

The purpose of PQ is to establish that the installation and all its systems and subsystems operate effectively and consistently when the storage area is *fully operational* (in use, loaded with TTSPPs). PQ is normally carried out immediately after satisfactory completion of the IQ and OQ stages. As previously noted, once the entire OQ and PQ process has been successfully completed and all deviations have been corrected, the installation can be signed off and fully released for routine operation.

A PQ inspection should:

- Check that all controllers and sensors are correctly calibrated.
- Carry out a temperature mapping of the storage area loaded as in normal operations. Record the results. See Technical Supplement: *Temperature mapping of storage areas*.
- Test and record temperature recovery following a door opening during normal operation.

2.6.1 Checking installed systems, subsystems and components

As with the IQ procedure described in section 2.4.2 and the OQ inspection in section 2.5.1, the PQ inspection and test tables and report should record the *specified condition* and the *as found* conditions and should confirm whether the as found condition is a *pass* or a *fail*. All *deviations* should be recorded, and the assessment results should be signed by the inspector and checked by the independent reviewer.

2.6.2 Temperature mapping – full

The temperature mapping exercise described in section 2.5.6 is repeated as for OQ, but with the storage area loaded normally with TTSPPs. The same arrangement of EDLMs should be used for the PQ mapping as for the OQ mapping.

2.6.3 Temperature recovery after door opening

The purpose of the door opening temperature recovery test is to establish that the temperature within the store can return to being within the specified temperature range within the specified time following a door opening event. The following test parameters should be observed:

- The same arrangement of EDLMs should be used as for the OQ and PQ mapping tests.
- The door-open period used for the test should represent actual door opening behaviour observed during routine operations. If there is a single door, the critical factor is the maximum observed length of opening. If there is more than one door, the critical factors are the length of opening, the sequence of opening, and whether more than one door needs to be kept open at the same time.

The acceptance criterion for this test is that the temperature recorded by all the EDLMs located inside the storage area should return to being within the specified temperature range (e.g. 2.0 °C to 8.0 °C within 30 minutes after the door(s) are closed at the end of the door opening test sequence). Table 10 shows an example of a door opening test sheet.

Table 10
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		☐	☐		

Table 10 *continued*

Door(s) opened at (hh:mm):			
Door(s) closed at (hh:mm):			
Checked by:		**Date:**	

2.6.4 Writing the PQ report

As soon as the PQ assessment has been completed, prepare a report as outlined in section 2.2.1. Pay particular attention to doing the following:

- Make sure that all of the sections included in the PQ protocol have been completed, signed and dated.
- Record all deviations from the installation drawings and specifications in the deviation report section. Make sure that each deviation is cross-referenced to the relevant sections of the PQ protocol.
- Transcribe any handwritten notes made by the PQ team into the relevant sections of the report.
- Specify the actions that need to be taken to correct the reported deviations and state the person or organization responsible for completing these actions.
- List all members of the qualification team, and their designations.

The installation cannot be formally released for routine use until all of the deviations recorded during the PQ inspection have been corrected.

2.7 Specific requirements for small-scale equipment

Cabinet freezers and refrigerators are frequently used for storing TTSPPs in smaller facilities such as pharmacies and health-care facilities. This equipment may include domestic freezers and refrigerators,[11] vaccine freezers and refrigerators,[12] blood bank refrigerators and specialist pharmacy and laboratory refrigerators and freezers. Capacities can vary from as little as 10–15 litres up to 1000 litres or more for a large pharmacy refrigerator.

[11] Domestic refrigerators do not control temperature accurately and WHO specifically recommends that they should not be used for storing vaccines, many of which are damaged by freezing.

[12] See the WHO PQS website at: http://apps.who.int/immunization_standards/vaccine_quality/pqs_catalogue/

With the exception of domestic equipment, these products are thoroughly tested to meet the specific needs of the medical applications for which they were designed. However, the working environment in which such equipment is ultimately placed may expose it to operating conditions outside its design envelope – examples of such conditions include very high or very low ambient temperatures, humid tropical conditions, extended power cuts and the like.

Consequently it may be necessary to carry out an IQ,, OQ, PQ test sequence, or some subset of this process, to establish that a specific product is fit for purpose in the actual operating environment. In particular, some form of temperature mapping may be needed; this should definitely be done in the case of domestic equipment. In this case, EDLMs should be used to record temperatures at the top and bottom of the cabinet as well as at the rear and front. Door shelves should not be used to store TTSPPs because this zone is known to be subject to widely fluctuating temperatures.

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Revision history

Date	Change summary	Reason for change	Approved

Annex 1

Deviation and corrective action report form

Report number:	
DEVIATION DESCRIPTION	
Documented by:	Date:
IMPACT ASSESSMENT ON QUALIFICATION	
Does this deviation have sufficient impact on the qualification to require a corrective action?	Yes ☐ No ☐
Documented by:	Date:
RATIONALE FOR CORRECTIVE ACTION	
Documented by:	Date:
CORRECTIVE ACTION APPROVAL	

Name	Signature	Date

RATIONALE FOR CLOSING THE DEVIATION REPORT

Does corrective action resolve the deviation? (Attach all resulting test data sheets to this report)	Yes ☐ No ☐ Not applicable ☐
Can this deviation be closed?	Yes ☐ No ☐

Name	Signature	Date

Supplement 8

Temperature mapping of storage areas

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

Annex 9: Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products

May 2015

Contents

Abbreviations

3PL	third-party logistics (provider)
CAPA	corrective and preventive action (procedures)
EDLM	electronic data logging monitor
GMP	good manufacturing practice
IQ	installation qualification
NIST	National Institute of Standards and Technology (US)
SLA	service level agreement
SOP	standard operating procedure
TTSPP	time- and temperature-sensitive pharmaceutical product

Acknowledgements

The author of this document is Jean Bédard, President and Chief Executive Officer, Infitrak Inc.

Glossary

Component: Any major piece, part or assembly of the main equipment or sub-equipment that does not have its own power supply and could not operate as a stand-alone unit (valves, or switches).

Controller: A device that interprets a mechanical, digital or analogue signal, generated by a sensor, to control an item of equipment or component.

Deviation: For installation qualification: any discrepancy between the installation specifications and the actual (as found) installation. For operational qualification: any discrepancy between the protocol and the actual performed test, test function methodology, testing equipment, and testing material.

Electronic data logging monitor (EDLM): A small portable device that measures and stores temperature readings at predetermined time intervals by means of an electronic sensor. They have programmable alarm capabilities, integrated displays, and can create reports and graphs which may be permanently stored, shared and analysed via proprietary hardware, software, desktop application or through hosted databases.

Installation qualification (IQ): The process of obtaining and documenting evidence that the premises, equipment and supporting systems have been provided and installed in compliance with their design specifications.

Instrument: A device that interprets a mechanical, digital or analogue signal generated by a sensor, and converts it into engineering units (°C, percentage relative humidity, mA, etc.) through scaling.

Key operating parameters: parameters that must be maintained in order to process or produce products with consistent quality attributes and those that may have an impact on the proper operation of the equipment.

Main equipment: Major equipment to be qualified.

Mapping: Documented measurement of the temperature and/or relative humidity distribution within a storage area, including identification of hot and cold spots.

Operational qualification (OQ): The process of obtaining and documenting evidence, under controlled conditions, that the premises, equipment and supporting systems operate in accordance with their design specifications.

Performance qualification (PQ): The process of obtaining and documenting evidence that the premises, equipment and supporting systems, as connected together, will consistently perform in accordance with the approved process method and specifications.

Pharmaceutical product: Any product intended for human use or veterinary product intended for administration to food producing animals, presented in its finished dosage form, that is subject to control by pharmaceutical legislation in either the exporting or the importing state and includes products for which a prescription is required, products which may be sold to patients without a prescription, biologicals and vaccines. Medical devices are not included.[1]

Refrigeration equipment: The term "refrigeration" or "refrigeration equipment" means any equipment whose purpose is to lower air and product temperatures and/or to control relative humidity.

Sensor: A mechanical device (pressure switch, bimetal temperature switch, etc.), or a digital or analogue transducer (limit switch, pressure sensor, temperature sensor, etc.) that generates a mechanical or electrical signal to an instrument or a controller in order to be interpreted.

Service level agreement (SLA): A service level agreement or contract is a negotiated agreement between the customer and service provider that defines the common understanding about materials or service quality specifications, responsibilities, guarantees and communication mechanisms. It can either be legally binding, or an information agreement. The SLA may also specify the target and minimum level performance, operation or other service attributes.[2]

Standard operating procedure (SOP): A set of instructions having the force of a directive, covering those features of operations that lend themselves to a definite or standardized procedure without loss of effectiveness. Standard operating policies and procedures can be effective catalysts to drive performance improvement and improve organizational results.

Storage temperature: The temperature range listed on the TTSPP label, and within the regulatory filings, for long-term storage.

Temperature-controlled: Includes any environment in which the temperature is actively or passively controlled at a level different from that of the surrounding environment within precise predefined limits.

Time and temperature-sensitive pharmaceutical product (TTSPP): Any pharmaceutical good or product which, when not stored or transported within predefined environmental conditions and/or within predefined time limits, is degraded to the extent that it no longer performs as originally intended.

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[1] Definition from WHO/QAS/08.252 Rev 1 Sept 2009. *Proposal for revision of WHO good distribution practices for pharmaceutical products – Draft for comments*.

[2] Definition from International Air Transport Association (IATA). 2013/2014 Perishable cargo regulations (ePCR) & temperature control regulations (eTCR). Geneva: IATA.

Validation: Documented testing performed under highly controlled conditions, demonstrating that processes, methods, and systems consistently produce results meeting predetermined acceptance criteria.[3]

[3] Parenteral Drug Association. PDA Technical Report No. 39: Guidance for temperature controlled medicinal products: maintaining the quality of temperature-sensitive medicinal products through the transportation environment. Berlin: PDA; 2007.

1. Introduction

This technical supplement has been written to amplify the recommendations given in section 4.7 of WHO Technical Report Series No. 961, 2011, Annex 9: *Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products*.[4] The purpose of a temperature mapping study is to document and control the temperature distribution within a storage area.

This document describes how to carry out a systematic mapping procedure in any cold room, freezer room or other temperature-controlled store. It does not cover mapping of small-scale cold chain equipment such as refrigerators or freezers. Generally speaking, these products are independently tested and prequalified for the storage of TTSPPs, although it is still important that the equipment is correctly installed and operated.[5]

The following Technical Supplements are also relevant:

- *Checking the accuracy of temperature control and monitoring devices*
- *Qualification of temperature-controlled road vehicles*
- *Qualification of temperature-controlled storage areas*
- *Temperature and humidity monitoring systems for transport operations.*

1.1 Requirements

All new temperature-controlled storage areas must be temperature-mapped as part of a fully documented verification process, before the installation is commissioned and handed over by the installer. Until this has been done, it is not safe to store TTSPPs in such areas. The temperature mapping procedures should:

- demonstrate the air temperature profile throughout the storage area, when empty and in a normal loaded condition;
- define zones which should not be used for storage of TTSPPs (for example areas in close proximity to cooling coils, cold air streams or heat sources); and
- if required, demonstrate the time taken for temperatures to exceed the designated limits in the event of a power failure.

Depending upon the routine monitoring strategy, subsequent mapping exercises may also be required periodically – for example, every three years – in order to demonstrate continuing compliance. In situations where multiple

[4] http://apps.who.int/medicinedocs/documents/s18683en/s18683en.pdf

[5] See for example: http://apps.who.int/immunization_standards/vaccine_quality/pqs_catalogue/

fixed monitors provide continuous data, a periodic re-evaluation which assesses all aspects of system performance since the initial mapping may be more appropriate. In addition mapping should be carried out whenever significant modifications are made to the store. Examples include changes in the pattern of use that may increase loading or affect air circulation, or changes to the refrigeration equipment, such as an alteration to the set point. Finally re-mapping may be justified whenever an analysis of temperature and/or humidity monitoring records shows unexplained variability outside normal operating limits.

All mapping exercises should be fully documented in order to demonstrate compliance to management, clients and the regulatory authorities.

1.2 Objectives

The objective of this Technical Supplement is to provide clear guidance on how to conduct a temperature-mapping study in a temperature-controlled storage area. This guidance applies to any space designed for long-term or short-term storage of TTSPPs or other temperature-sensitive products.

1.3 Target readership

This document is relevant to wholesalers, warehouse operators, distributors, dispatchers and third-party logistics providers (3PLs) who store and distribute TTSPPs. The specific target audience within these organizations includes those who have direct responsibility for quality management, for example, quality assurance (QA) managers and operations managers.

2. Guidance

A temperature-mapping exercise is required for any space allocated for the storage and handling of products with a specified labelled storage temperature. This includes freezer rooms, cold rooms, temperature-controlled storage areas, quarantine areas and receiving and loading bays. It may also include laboratories. The permitted temperature ranges in these areas will vary – for example: −25.0 °C to −10.0 °C, 2.0 °C to 8.0 °C, or 15.0 °C to 25.0 °C. Temperature-mapping may also need to be carried out in spaces without active temperature control.

A mapping study establishes the temperature distribution within the zone being mapped and locates hot and cold spots. The data collected provide an essential source of information to ensure that all TTSPPs are correctly stored within their labelled temperature range(s). Mapping may also be used to identify zones where remedial action is needed; for example by altering existing air distribution to eliminate hot and cold spots, or by retro-fitting new air distribution equipment to reduce temperature stratification in high-bay warehouses.[6]

The temperature-mapping process has four stages:

a. Prepare a mapping protocol.
b. Carry out the mapping exercise.
c. Prepare a mapping report.
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.

2.1 Associated materials and equipment

A mapping operation requires a sufficient number of electronic data logging monitors (EDLMs) to ensure that the temperature distribution in the space to be mapped is adequately characterized. In addition, suitable computer equipment and software is needed to store and analyse the data. The selected EDLMs must:

- be technically suitable for the specific mapping task and for the intended operating environment;
- provide a reliable and continuous record of time-temperature data;
- have an appropriate temperature range so that all anticipated temperature extremes can be recorded (e.g. from −30 °C to +60 °C);

[6] High bay pallet racking stores are particularly susceptible to temperature stratification. It is essential that such stores are comprehensively mapped over their full working height.

- have a user-programmable data sampling period, allowing time intervals to be set in the range from 1 minute to 15 minutes (maximum) and sufficient memory for the intended length of the study and the chosen recording interval;
- have a US National Institute of Standards and Technology (NIST)-traceable 3-point calibration certificate with a guaranteed error of no more than ± 0.5 °C at each calibration point;
- enable the recorded time-temperature data to be downloaded to a computer system for subsequent analysis;
- have data storage and analytical software that complies with applicable regulatory requirements (for example: 21 CFR part 11).[7,8,9]

2.2 The mapping protocol

A detailed and comprehensive protocol should be prepared, reviewed and approved before the mapping exercise begins. A well-designed protocol will help ensure that the mapping study is correctly carried out. With suitable adjustments or options to cover the full range of temperature regimes, a standard protocol can be used to map any storage area in the facility.

The mapping protocol should contain the following sections:

a. Approval page and change control history
b. Acronyms and glossary
c. Description and rationale
d. Scope
e. Objectives
f. Methodology
g. Mapping report template
h. Annexes as needed, including templates for the mapping report.

The content of each of these sections is detailed below.

2.2.1 Approval page and change control history

Include a standard template for recording approvals and changes to the document. Table 1 provides an example.

[7] United States Pharmacopeia: Chapter 1079: Good storage & shipping practices.
[8] United States Pharmacopeia: Chapter 1118: Monitoring devices – time, temperature and humidity.
[9] US Food & Drug Administration (FDA): 21 CFR part 11.

Table 1
Example of standard template for approvals and changes to the 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			

If the protocol has been prepared by a qualified third party, it should be authorized by the responsible person within the commissioning organization.

2.2.2 Acronyms and glossary

Define the acronyms and technical terms used in the protocol.

2.2.3 Description and rationale

Describe the installation to be mapped and outline the reasons for carrying out the exercise.

2.2.4 Scope

Clearly define the scope and purpose of the mapping study. The fundamental purpose is to identify temperature deviations affecting the chosen storage area(s) at the time the study is conducted, so that remedial action can be taken.

Depending upon the circumstances, a temperature-mapping study may be carried out in an empty storage area – for example during operational qualification of a new cold room – or in a storage area where TTSPPs are already being kept – for example after alterations have been made to an existing cold room. See Technical Supplement: *Qualification of temperature-controlled storage areas*.

If storage areas are affected by seasonal temperature variations, at least two temperature-mapping studies may be needed in each area to observe the effect of seasonal variation. Typically, one should be carried out during the warmest season and one during the coldest season. This will represent the worst-case scenarios and will establish whether the mapped area is able to maintain stable temperatures throughout the year. Typically, two-season mapping is not necessary for cold rooms and freezer rooms.

The results of the two studies can be compared so that systematic issues related to the season can be identified. These seasonal effects need to be separated from any other site-specific issues arising at the times when the comparative studies are done.

2.2.5 Objectives

The detailed objectives of the study should be clearly defined, and should include:

- Mapping of temperature variations within the selected storage areas. Typically these areas include freezer rooms, cold rooms and warehouses. Packing areas, loading bays and other areas in which temperature-sensitive products are stored, or are temporarily held when in transit may also be mapped and monitored, although temperatures in these areas are likely to fluctuate when doors are opened.
- Measuring temperature variations at each location within the chosen area, by day of the week and time of day.
- Documenting high and low temperature fluctuations caused by the environmental control systems operating at the time of the study – for example, heating, cooling and ventilation.
- Identifying potential airflow issues that may be the cause of temperature variations.
- Recommending where TTSPPs can safely be stored in the mapped area and where they must *not* be stored. These recommendations should take account of any temperature deviations identified during the study as well as the approved temperature range(s) for the products being stored in the area.
- Identifying the best places to locate temperature sensors for routine monitoring in circumstances in which a monitoring system is to be installed. If a monitoring system is already installed, identify the best places to relocate temperature sensors (if necessary).
- Making recommendations for any remedial actions needed to overcome the problems identified in the study.

2.2.6 Methodology

The methodology for conducting a temperature mapping study involves the following steps. It is important to note that steps 1 to 5 must be completed *before* the mapping protocol can finally be approved.

Step 1 – select EDLMs: Select the type of EDLM to be used. Choose a device that has sufficient memory for the intended duration of the study and the selected recording interval. As noted in section 2.1, all loggers must have a NIST-traceable 3-point calibration completed and valid (within the current year), and have an error of no more than ± 0.5 °C at each calibration point. Valid calibration certificates for each of the data loggers used in the study must be included in the mapping report. Some EDLMs with built-in batteries and a limited life are not designed to be recalibrated; otherwise calibration should be done annually.

Calibration temperature points used for the calibration of EDLMs should cover the required temperature range for each of the areas being studied. In general there should be one calibration point below the low end of the range, one calibration point in the middle of the range, and one calibration point above the high end of the range.

To ensure consistency, use only one type of device per mapping study. Provide a link to the manufacturer's user instructions so that those responsible for programming and reading the devices understand how to perform these actions correctly.

It may be appropriate to include an EDLM device that is able to monitor door openings, programmed so that the readings on the temperature monitoring devices can be aligned with door opening times.

Step 2 – designate the mapping team: Identify and list the team members. Record their signatures and initials so that signed records can be traced back to the person who prepared the document. Ensure that all team members receive the training needed to perform their assigned tasks.

Step 3 – survey the site: Conduct a site survey of the area(s) to be mapped. The following information is required for each thermally separate area being mapped:

- length, width and height;
- drawing of each area, showing elements, such as shelving or pallet racking, that may have an effect on the even heating or cooling of the space and which may affect its temperature stability. The shelving or pallet racking will be used to place the EDLMs, so it is important to record these components accurately;
- the location of heating and cooling components, including air distribution outlets and/or ceiling fans;
- the location of existing temperature recording sensors and temperature controlling sensors.

Step 4 – establish acceptance criteria: The protocol should define the required acceptance criteria, based on the type of TTSPPs being stored, clearly stating the temperature limits that are allowable within the area to be mapped – for example: +2.0 °C to +8.0 °C or +15.0 °C to +25.0 °C. However, some mapping studies may be performed without predefining any acceptance criteria. This type of study can be used to establish the types of product that can safely be stored in a specific space, and what remedial actions might have to be taken to improve the thermal performance of the space in order to optimize its use.

If the temperature-mapping study is designed to include door opening(s), this should be stated in the study methodology and acceptance criteria. Also the door opening parameters (frequency and duration) should be defined. The temperature should be maintained within the defined temperature limits except for a maximum of 30 minutes following the door opening.

Step 5 – determine EDLM locations: Use the site survey to mark the required locations of the EDLMs. A risk-based approach can be applied to define these locations. However, the following guidelines will help determine the number and location of the EDLMs required.

Length and width: EDLMs should be arranged in a grid fashion along the width and length of the area so that the area is reasonably covered, with EDLMs located every 5–10 metres.[10] The chosen sensor grid should take account of:

- the layout of the area (e.g. whether it is square or includes alcoves);
- the degree to which shelving and products may affect airflow;
- where products are placed. The positions of EDLMs should coincide with locations where TTSPPs are actually stored or planned to be stored. For example, it may be unnecessary to fit EDLMs in areas such as the upper part of high loading bays;
- other considerations that may warrant more or fewer EDLMs.

Height: At each point on the grid, arrange EDLMs vertically as follows:

- If the ceiling height is 3.6 metres or less, position EDLMs directly above one another at high, medium and low level (e.g. one EDLM at floor level, one at 1.2 metres and one EDLM at 3.0 metres.
- If the ceiling height is greater than 3.6 metres, EDLMs can be arranged in vertical arrays at the bottom, middle (multiple) and top of the space. For instance, for a storage area 6 metres in height, EDLMs can be positioned in each grid location at heights of 0.3 metres, 1.8 metres, 3.6 metres and 5.4 metres.

[10] In very large facilities, this can be up to 20 or 30 metres.

Give each logger location a unique ID. It may be helpful to use a generic floor plan or diagram to decide where each logger should be positioned – see Figures 1 and 2. Figure 1 shows part of a pallet racking cold room with an adjoining temperature-controlled packing area. Figure 2 shows a small walk-in cold room with products stored on shelves – the shelves (on which the EDLMs should be placed) have been omitted for clarity. If products are also stored on pallets in the centre of the room, additional EDLMs should be placed in this location.

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

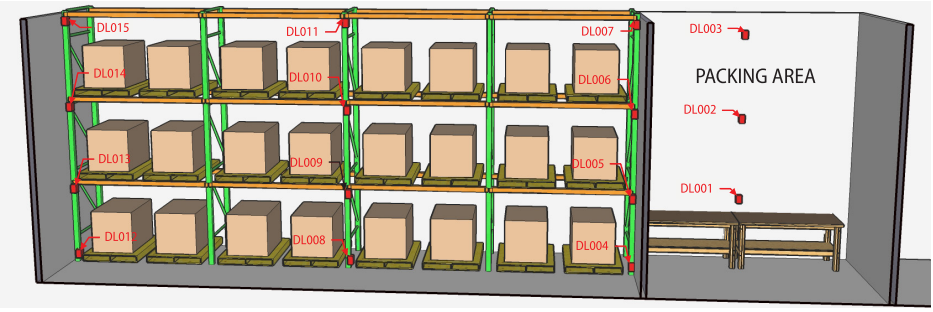
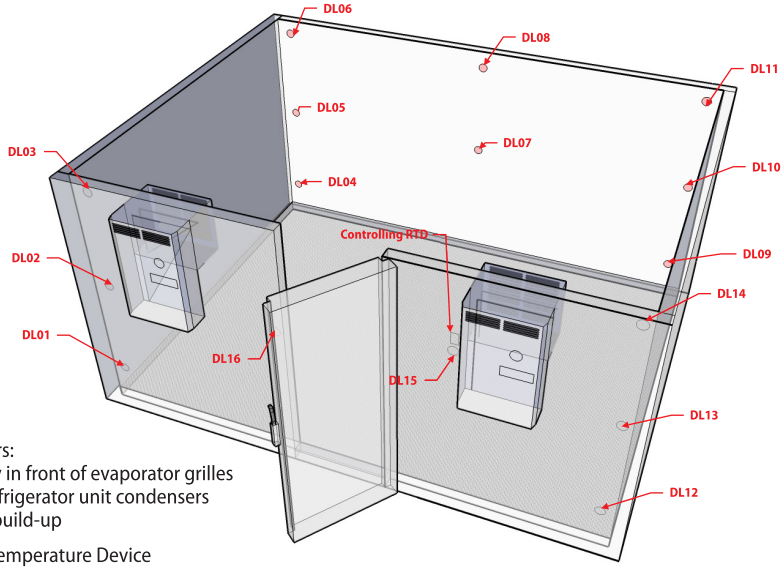


Figure 2
Typical location of data loggers in a walk-in cold room



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

Step 6 – record EDLM, monitoring sensors and thermostat locations: Record the EDLM locations on a temperature data logger location table – see example in **Annex 1.1**. Also record the location identification and set point for each thermostat in the storage area – see example in **Annex 1.2**.

Step 7 – label and program the EDLMs: Label each EDLM with a unique ID, taken from the temperature data logger location table. Enter the manufacturer's serial number on the temperature data logger location table (**Annex 1.1**). Recording the serial number ensures that the device can be traced to its calibration certificate. Program each device, ensuring that the recording interval is the same – typically this should be set between 1 and 15 minutes. Set the same start time for all units. This is *essential*; otherwise the readings downloaded from the individual devices cannot be time-correlated. Make sure that the start time setting allows enough time for all the units to be fixed in position before recording begins.

Step 8 – fix EDLMs in position: Fix the EDLMs in position making sure that each one is placed exactly as shown on the temperature data logger location table and drawing. Position and fasten the devices so that they cannot be damaged or displaced during the course of routine store operations. Ensure that sufficient time is allowed for the EDLMs to be conditioned to the ambient temperature before the mapping exercise begins.

Step 9 – conduct the mapping exercise: There is no formal time limit for a mapping study. Typically, for warehouses and other ambient storage areas, it should be run for a minimum of seven consecutive days – including five working days and two weekend days. For temperature-controlled equipment which is not critically affected by diurnal or seasonal variations in ambient temperature (e.g. freezer rooms and cold rooms), the mapping study should be run for between 24 and 72 hours, or longer if justified. If the room is fitted with duplicate refrigeration units – with or without automatic changeover – it is essential to map temperatures over a period that includes the operation of both units running separately; preferably for a similar time period. The temperature distribution in the room may vary depending upon which system is running.[11]

At the end of the study, collect the EDLMs and double-check their serial numbers and locations against the installation notes.

Step 10 – download and consolidate the data: Download the EDLM readings and consolidate the data for the analysis described in section 2.4.

[11] Duplicate units are sometimes set up so that one system runs most of the time and the other only cuts in at a higher temperature. This ensures that the second unit runs infrequently and therefore reduces the chances of a simultaneous breakdown.

2.2.7 Mapping report template

The mapping report should include the following sections:

a. *Introduction:* a description of the objectives of the mapping study.
b. *Summary:* a summary and discussion of the results organized in the sequence set out in the mapping protocol, including a summary of deviations (if any).
c. *Conclusions and recommendations:* a general conclusion for all verifications and observations indicating the acceptability of the equipment for operation. Recommendations and remarks can be incorporated in this section.
d. *Report annexes:* The annexes to the report should contain the following:
   - the site survey, showing EDLM locations;
   - the raw data, presented using the appropriate test data sheet format – see **Annex 1**.
   - spreadsheet data and related temperature graphs for every EDLM used in the mapping exercise;
   - raw results of the data analysis, including hot and cold spots;
   - key documents and notes prepared during the mapping exercise, together with any other supporting material;
   - deviation reports, including corrective and preventive actions (CAPA) forms, if required: this may include a recommendation for partial or total re-mapping;
   - calibration certificates for all EDLMs used.

2.3 Conducting the mapping exercise

Conduct the mapping exercise in accordance with the protocol. Ensure that all relevant personnel in the store are fully briefed so as to avoid inadvertent disruption or deactivation of the EDLMs. At the end of the study period, collect all the devices, deactivate them, and download the data for analysis.

If the mapping exercise does not include automatic logging of door openings, an access log should be kept during the study so that any temperature excursions caused by personnel movement can easily be identified. Power outages should similarly be recorded.

2.4 Analysing the data and preparing the mapping report

The mapping report should follow the general template outlined in section 2.2.7. The following subsections outline the data analysis process that precedes the writing of the report.

2.4.1 Preliminary analysis

Analyse the overall temperature stability of the study area and identify the variations that occur. Compare the measured temperatures against the acceptance criteria. The analysis of the overall temperature stability should consider factors such as:

- the ability of the environmental control systems to maintain temperatures within the acceptance criteria limits (if any);
- the overall temperature stability of the area being monitored, and the range in fluctuations it experiences over the study period;

The analysis of temperature variations should consider factors such as:

- variations experienced by individual EDLMs;
- temperature variations along vertical and horizontal planes, depending on the size of the area, and distribution of EDLMs;
- temperature variations in locations close to heating and cooling components, as compared to those farthest away from these units.

2.4.2 Minimum and maximum temperatures and hot and cold spots

A mapping study measures temperature fluctuations. From these data, the analyst can identify the minimum and maximum temperatures that occur in the mapped area during the study period.

Minimum temperature refers to the lowest temperature recorded in the mapped space over the study period; maximum temperature refers to the highest value recorded during the same period. Either or both of these temperatures may be outside the specified acceptance criteria for the store. **Annex 1.3** shows a standard form that can be used to record these data, together with the mean values discussed in section 2.4.4.

A cold spot refers to the lowest temperature(s) recorded in the space over the study period, but these lowest temperature(s) remain within the specified temperature range (e.g. cold spots identified between +15.0 °C and +17.5 °C in a room with a specified temperature range of +15.0 °C to +25.0 °C).

A hot spot refers to the highest temperature(s) recorded in the area studied over the study period, but these highest temperature(s) remain within the specified temperature range (e.g. hot spots identified between +23.0 °C and +25.0 °C in a room with a specified temperature range of +15.0 °C to +25.0 °C).

The purpose of determining hot and cold spots is to identify the locations where the monitoring system sensors should preferentially be located. Hot and cold spots need to be determined seasonally as they may be significantly different in summer and in winter. *Note:* It is also important to look at the overall high and low trends rather than just the highest and lowest temperatures. Average values can be useful to help confirm true hot and cold spots.

2.4.3 Mean temperatures

Arithmetic mean temperatures can be applied to each of the separate areas being monitored over the study period. These mean temperature measurements can be useful in storage areas where the temperature fluctuates with time in a repetitive pattern (e.g. sinusoidal fluctuation or periodic peak occurrence) and where the temperature also varies depending upon the location of the data logger.

The use of mean temperatures enables the analyst to determine a mean temperature for a given EDLM location over the study period. These figures can then be compared between all the EDLM locations within the space. This enables the analyst to identify the locations where the mean temperatures are consistently lower or higher, an outcome that cannot be achieved simply by comparing individual data points.

In Figure 3, the minimum and maximum temperatures have been calculated from the data points for two locations (EDLM-1 and EDLM-2). The plot shows that the EDLM-2 location is clearly cooler on average, although there are also times when the two locations experience similar low and high temperatures.

Despite the usefulness of mean figures, it is essential not to disregard the actual temperature data because these figures reveal the occurrence of temperatures that are outside the specified storage temperature range.

2.4.4 Interpreting the results and making recommendations

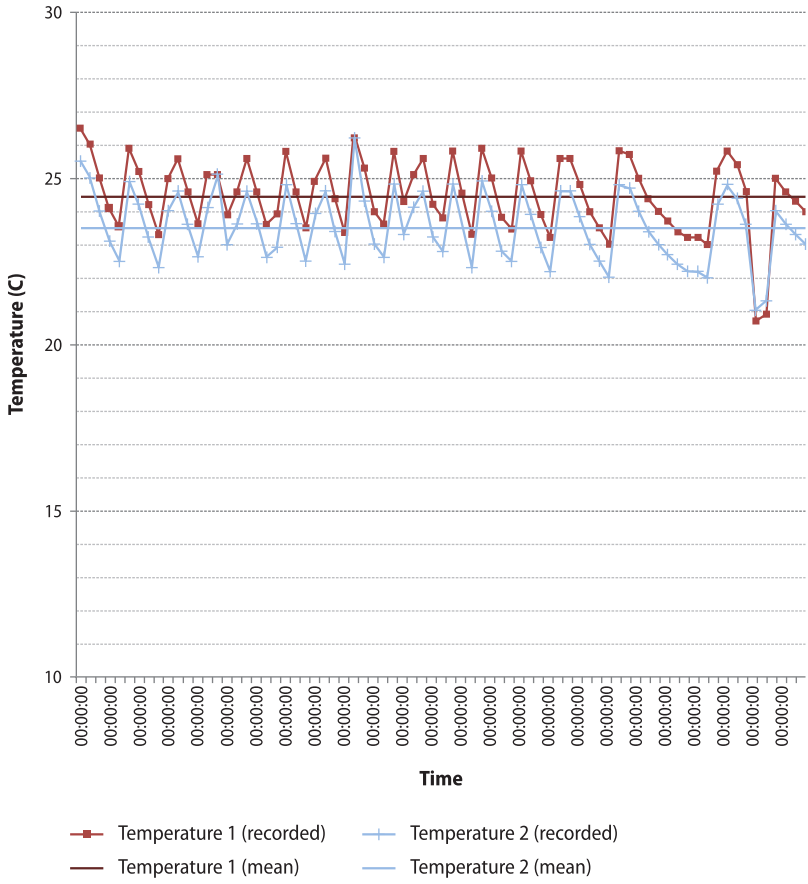
This section outlines how to interpret the results, and how to use these results to support the report's recommendations:

- Document the internal temperature variations observed within the space, taking account of the EDLM reading errors specified by the device manufacturer.
- Use the data analysis to assess the overall temperature stability of the mapped space in relation to the stated acceptance criteria (if any).
- Assess the overall thermal stability of the space during the study period with specific reference to the high and low temperatures experienced.
- List the factors that explain the observed temperature variations. For example, the location of the heating and cooling components and doors.[12]

[12] Thermal stability will be affected by three main factors: the external ambient temperature; the type of building construction and the performance of the heating or cooling system. The first two factors are less significant for freezer rooms and cold rooms built inside an existing structure.

- Assess consistent and inconsistent temperature variations and fluctuations within the space in terms of their potential impact on product storage.
- Based on the observed temperature fluctuations at the mapped locations within the space, make recommendations about the optimum storage locations for highly sensitive products, and those that are less sensitive.
- Based on the observed temperature fluctuations at the mapped locations within the space, make recommendations on the optimum location of the temperature sensor(s) used for routine temperature monitoring and the control sensors used to activate the heating and cooling systems.

Figure 3
Use of mean temperatures



2.4.5 Report auditing

The report's content, including data sheets, results, spreadsheets and graphs should be audited and peer-reviewed by a competent independent person. The reviewer should confirm, approve and sign the major reported test and verification results and the recommendations arising from these results. If the report has been prepared by a qualified third party, it should be approved by the person who commissioned the study.

2.5 Implementing the mapping report recommendations

The final outcome and purpose of a mapping exercise is the implementation of the report recommendations. A detailed discussion of implementation is outside the scope of this document, but it could include any of the following outcomes:

- A drawing or diagram showing where TTSPPs can safely be stored in the space that has been mapped: It is possible that there may be some zoning involved. For example, products that are not affected by freezing could be allocated to parts of a cold room where the mapping study has shown some freezing risk.
- Allocation of pallet bays to specific categories of TTSPP on the warehouse management system in order to control where stocks are positioned.
- Repositioning of temperature monitoring sensors and/or environmental control sensors.
- Adjustment of air outlets to reduce temperature stratification and/or minimize cold and hot spots.
- Upgrading of mechanical systems to improve temperature control and performance.
- A decision to use the space for other purposes because it is unsuitable for storage of TTSPPs.

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Annex 1

Test data sheets

The following sections show examples of the type of data collection forms used in a mapping exercise.

A1.1 Test data sheet: temperature data logger locations

Data logger ID number	Data logger serial number	ID number on schema	Mounting height (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	
DL-010		10	0.3	
DL-011		11	2.8	
DL-012		12	5.4	
DL-013		13	0.3	
DL-014		14	2.8	
DL-015		15	5.4	
DL-016		16	0.3	
DL-017		17	2.8	
DL-018		18	5.4	
DL-019		19	0.3	

Table *continued*

Data logger ID number	Data logger serial number	ID number on schema	Mounting height (metres)	Description/comments
DL-020		20	2.8	
DL-021		21	5.4	
DL-022		22	0.3	
DL-023		23	2.8	
DL-024		24	5.4	

A1.2 Test data sheet: temperature distribution

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

A1.3 Test data sheet: temperature distribution

Data logger ID number	Minimum temp. recorded (°C)	Maximum 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				☐	☐		
DL-010				☐	☐		
DL-011				☐	☐		
DL-012				☐	☐		
DL-013				☐	☐		
DL-014				☐	☐		
DL-015				☐	☐		
DL-016				☐	☐		
DL-017				☐	☐		
DL-018				☐	☐		
DL-019				☐	☐		
DL-020				☐	☐		
DL-021				☐	☐		
DL-022				☐	☐		
DL-023				☐	☐		
DL-024				☐	☐		

Table *continued*

Mapping period starts at (date/hour):	
Mapping period ends at (date/hour):	
Checked by:	Date:

Revision history

Date	Change summary	Reason for change	Approved

Supplement 9

Maintenance of refrigeration equipment

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

Annex 9: Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products

May 2015

Contents

Abbreviations

ATP	Agreement on the International Carriage of Perishable Foodstuffs and on the Special Equipment to be Used for such Carriage
CFC	chlorofluorocarbons
ECE	See also *UNECE*
GRP	glass reinforced plastic
GWP	global warming potential
HCFC	hydrochlorofluorocarbons
LSP	logistics service provider
ODP	ozone depletion potential
PTI	pre-trip inspection
SOP	standard operating procedure
TTSPP	time- and temperature-sensitive pharmaceutical product
UNECE	United Nations Economic Commission for Europe
ULD	unit load device

Acknowledgements

The author of this document is Richard Lawton, Technical Director, Cambridge Refrigeration Technology, Cambridge, England.

Glossary

Active systems: Externally powered or on-board powered systems using electricity or another fuel source to maintain a temperature-controlled environment inside an insulated enclosure under thermostatic regulation (e.g. cold rooms, refrigerators, temperature-controlled trucks, refrigerated ocean and air containers).

Passive systems: Systems which maintain a temperature-controlled environment inside an insulated enclosure, with or without thermostatic regulation, using a finite amount of preconditioned coolant in the form of chilled or frozen gel packs, phase change materials, dry ice or others.

Pharmaceutical product: Any product intended for human use or veterinary product intended for administration to food producing animals, presented in its finished dosage form, that is subject to control by pharmaceutical legislation in either the exporting or the importing state and includes products for which a prescription is required, products which may be sold to patients without a prescription, biologicals and vaccines. Medical devices are not included.[1]

Refrigerated container or reefer: A thermally insulated shipping container or intermodal freight container, equipped with an integrated refrigeration unit, used for the transport of TTSPPs, by road, rail or ocean freight. The refrigeration unit requires an external electrical power supply when located at a land based site, on a container ship or on a quay. During road transport electrical power is typically supplied by a diesel generator.

Refrigeration equipment: The term "refrigeration" or "refrigeration equipment" means any equipment whose purpose is to lower air and product temperatures and/or to control relative humidity.

Refrigerated vehicle: Road transport vehicle such as a van, truck or semi-trailer whose isolated thermostatically controlled cargo compartment is maintained at a temperature different (lower or higher) than the external ambient conditions. The environment inside the cargo compartment may be *temperature-controlled* or *temperature-modified*.

Service level agreement (SLA): A service level agreement or contract is a negotiated agreement between the customer and service provider that defines the common understanding about materials or service quality specifications, responsibilities, guarantees and communication mechanisms. It can either be

[1] Definition from WHO/QAS/08.252 Rev 1 Sept 2009. *Proposal for revision of WHO good distribution practices for pharmaceutical products – Draft for comments*.

legally binding, or an information agreement. The SLA may also specify the target and minimum level performance, operation or other service attributes.[2]

Standard operating procedure (SOP): A set of instructions having the force of a directive, covering those features of operations that lend themselves to a definite or standardized procedure without loss of effectiveness. Standard operating policies and procedures can be effective catalysts to drive performance improvement and improve organizational results.

Temperature-controlled: Includes any environment in which the temperature is actively or passively controlled at a level different from that of the surrounding environment within precise predefined limits.

Temperature-modified: Includes any environment in which the temperature is predictably maintained at a level different from that of the surrounding environment, but is not actively or passively controlled within precise predefined limits.

Third-party accreditation: Accreditation or certification by an organization that issues credentials or certifies third parties against official standards as a means of establishing that a contractor is competent to undertake a specific type of work. Third-party accreditation organizations are themselves formally accredited by accreditation bodies; hence they are sometimes known as "accredited certification bodies". The accreditation process ensures that their certification practices are acceptable, typically meaning that they are competent to test and certify third parties, behave ethically and employ suitable quality assurance.

Time and temperature-sensitive pharmaceutical product (TTSPP): Any pharmaceutical good or product which, when not stored or transported within predefined environmental conditions and/or within predefined time limits, is degraded to the extent that it no longer performs as originally intended.

[2] Definition from International Air Transport Association (IATA). 2013/2014 Perishable cargo regulations (ePCR) & temperature control regulations (eTCR). Geneva: IATA.

1. Introduction

This technical supplement has been written to amplify the recommendations in section 4.9 of WHO Technical Report Series No. 961, 2011, Annex 9: Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products.[3] It does not specifically deal with emergency maintenance or contingency planning. Related topics are covered in the following Technical Supplements:

- *Checking the accuracy of temperature control and monitoring devices*
- *Environmental management of refrigeration equipment*
- *Maintenance of storage facilities*
- *Temperature mapping of storage areas*

1.1 Requirements

Implement a maintenance programme for all temperature-controlled rooms, cold rooms, freezer rooms, refrigerators and freezers:

- Carry out regular preventive maintenance on all temperature-controlling equipment.
- Employ best practice to eliminate leakage of refrigerant into the environment during installation, maintenance and decommissioning of refrigeration equipment.

Records should be maintained to demonstrate compliance with the above requirements.

1.2 Objectives

The objective of this Technical Supplement is to provide guidance on how to meet the above requirements with regard to the maintenance of cold chain equipment for use with TTSPPs. The guidance covers all types of fixed and mobile temperature-controlling equipment.

1.3 Target readership

This technical supplement provides guidance on the maintenance of cold chain equipment aimed at more senior operations management staff. Principally these will be the owners and operators of warehouses, pharmacies and other stores, and owners and operators of refrigerated vehicles used to store and transport TTSPPs.

[3] http://apps.who.int/medicinedocs/documents/s18683en/s18683en.pdf

2. Guidance

This section provides general guidance on how to maintain the following categories of temperature-controlled equipment:

- active and passive insulated container systems used for transport;
- refrigerators and freezers;
- freezer rooms, cold rooms and controlled ambient stores;
- refrigerated vans;
- refrigerated rigid vehicles;
- refrigerated semi-trailers;
- refrigerated containers.

The sections below discuss the preventive maintenance requirements for each of these types of equipment.

2.1 Associated materials and equipment

Technicians should be appropriately equipped so that they are able to maintain temperature-controlled systems in an operable and safe condition. The basic equipment needed includes the following:

- refrigeration equipment service manuals;
- digital thermometer;
- cleaning equipment (non-solvent based);
- insulated envelope repair equipment (sealant, plating, pop riveter);
- multimeter for electrical testing;
- electronic leak detector (or sponge and soapy water);
- manifold gauges set and refrigeration tools;
- spare refrigerant;
- spare parts kits;
- refrigerant recovery machine and bottle;
- vacuum pump;
- weighing scales.

2.2 Active and passive transport containers

Reusable transportable insulated containers, such as cold boxes and the insulated unit load devices (ULDs) used for air transport,[4] are subject to wear and tear

[4] See: http://en.wikipedia.org/wiki/Unit_load_device

because they are handled frequently. Maintenance is likely to be limited to washing the interior and exterior with a solution of mild soapy water or a disinfectant solution containing sodium hypochlorate, 5.25% in water.

Some repairs to cold boxes may be possible, but end of life for this category of equipment will be indicated when there are holes or cracks in the internal and external covering which expose the insulating core.

Cooling elements for passively cooled containers include frozen water-packs, cool water-packs, phase-change material (PCM)-packs or eutectic plates, and possibly dry ice (solid carbon dioxide). Smaller actively cooled containers may use electronic Peltier systems. Larger actively cooled containers may have mechanical refrigeration systems. Repairs to ULDs are routinely carried out at specialist repair stations located around the world, operated by the container manufacturers.

2.3 Refrigerators and freezers

Refrigerators and freezers comprise an insulated envelope. This is normally cooled by a sealed compression-cycle refrigeration system operating on mains electricity. In remote areas with no other power supply they may use photovoltaic power systems. Gas and kerosene absorption units are also used in such places. The maintenance of these small-scale off-grid systems is outside the scope of this document, but is covered in EVM-SOP-E5-03.

The cooling system can continue to run for many years. End of life is likely to occur as a result of degradation of the insulation (especially for freezers), door hinges, door seals or cracks in the internal or external covering. Terminal degradation to the insulation of freezers is indicated by the presence of condensation on the outside, or sometimes even by the presence of ice. When this occurs the equipment should be replaced. Another indication of insulation degradation is an excessively long compressor duty cycle; the cooling equipment runs continuously with the interior never reaching the set point.

Maintenance procedures, such as those listed in EVM-SOP-E5-03, should concentrate on cleaning:

- Keep clean by regularly washing with mild soapy water solution.
- Check operation of thermostat and defrost system (if fitted).
- Keep door seals clean, avoiding build-up of material between folds and at corners.
- Remove build-up of ice (use the defrost system or a blunt scraper).
- Keep drains free of debris.
- Check appliance level – give a small fall to the rear (no more than 4 mm) to ensure door closure.
- Clean condenser coil (fins), ensure fins and cooling fan and any grilles are free of dust, fluff and debris.

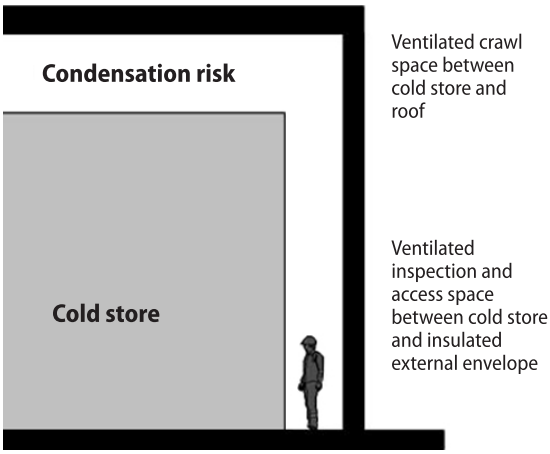
Repairs to the cooling system are likely to be uneconomical: once the pipework of a sealed mechanical system is broken into, the reliability is likely to be severely compromised. On a cost basis, where possible, it is advised that repairs be limited to electrical systems, thermostats, defrost timers and start relays; otherwise replacement of the refrigerator or freezer is recommended.[5]

In the case of absorption refrigeration systems, which are fully sealed and under relatively high pressure, repairs can only be made to the heater and thermostat, although inverting the entire refrigerator for a few hours can sometimes bring an apparently dead unit back to life.

2.4 Freezer rooms, cold rooms and controlled ambient stores

Freezer rooms, cold rooms and controlled ambient stores represent a considerable financial investment and should, with correct maintenance, last for 20–30 years. They consist of two main components: an insulated envelope constructed of preformed insulated sandwich panels and a vapour compression mechanical refrigeration system. The temperature for freezer rooms is generally −20 °C or below, for cold rooms it is +2 °C to +8 °C and for controlled ambient stores it is +15 °C to +25 °C. Figure 1 shows a typical cold store arrangement with a cold store built of insulated panels constructed inside an enclosing warehouse building. Larger cold stores may take structural support from the enclosing building; smaller units up to about 6 metres in span are generally self-supporting.

Figure 1
Layout of insulated envelope and weather enclosure



[5] Notwithstanding these recommendations, the skill and ingenuity of competent technicians can be impressive and systems may be repaired even where spares or new units are not readily available.

2.4.1 Maintenance overview

Cold stores are delivered by the constructer in working condition, verified by commissioning tests, thermal scans and third-party accreditation. To enable the intended design life to be achieved a well-considered programme of regular inspection and preventive maintenance should be put in place. Two elements of a cold store require maintenance: the refrigeration equipment and the insulated envelope. Close attention should be paid to both of these elements. It is essential not to neglect the insulated envelope, although in the short term this might appear less important.

Owing to their size, cold stores of all three types are likely to store products with a substantial total value. To minimize the risk of product loss, most cold stores should have a duplicate refrigeration system, an emergency power supply and a sophisticated temperature monitoring and alarm system, all of which also need to be maintained.

2.4.2 Maintaining the cooling system

Cooling systems require regular maintenance; see for example the procedures set out in EVM-SOP-E5-02.

When maintaining and testing systems, it is important to remember that product losses are just as likely to be caused by exposure to too low a temperature as by exposure to a high temperature. It is therefore necessary to check that the secondary system cuts in when the temperature exceeds the allowable maximum. The operating methodology and/or the control system should be designed so that the two refrigeration systems run alternately; this ensures that a problem with either system is quickly identified. The maintenance programme should also include checking the response of the system to temperatures below the allowable minimum. In particular there should be an independent cut-off mechanism to prevent low temperature excursions. For example, if the temperature is controlled by a solenoid valve system, the low-temperature safety system should cut off the power to the compressor.

2.4.3 Maintaining insulated panels and vapour control sealing

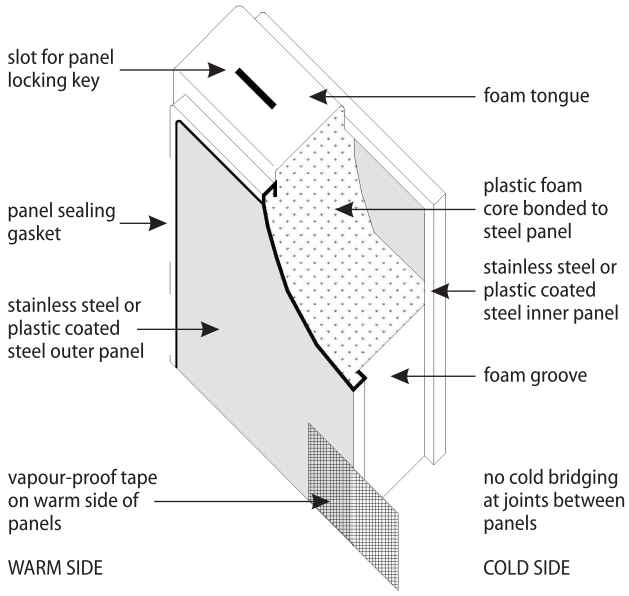
Maintenance programmes usually concentrate on the cooling equipment and the insulated envelope is frequently neglected. A badly maintained envelope will only last for 15 years; with good maintenance it can last twice as long.

Responsibility for the upkeep and the maintenance of the insulated envelope and vapour sealed panel joints should be given to a nominated person who has a clearly defined role to ensure that this work is carried out. There should be a comprehensive standard operating procedure (SOP) describing the appropriate maintenance and corrective work.

Cold store insulated envelopes are constructed from preformed insulated sandwich panels; typically corrosion-protected metal sheets with a core of foamed insulation. The insulated panels require a vapour control membrane to resist the infiltration of atmospheric water vapour into the insulation core. An impermeable barrier to prevent this happening is essential and can be likened to the hull of a ship. An ineffective vapour barrier will allow water vapour to penetrate, condense and freeze within the insulating core material or on the internal surfaces of the panels. This degrades the surfaces and leads to a loss of insulating effectiveness, panel delamination and possible structural collapse.

The metal facings of an insulating panel are themselves impermeable to water vapour transmission and effectively control the problem. The panel joints are the weak points because the joint itself must act as a vapour barrier. Continuity of the vapour control layer at the joints is achieved by incorporating a vapour seal. All joints should be sealed on the *warm* side of the enclosure, either by means of a proprietary sealing system supplied by the panel manufacturer, or with a mastic bead followed by a 100-mm wide strip of vapour-impermeable tape. Figure 2 shows a typical joint assembly.

Figure 2
Example of a cold store panel joint



Generally the panel seal only needs to be continuous on the warm side. It is not necessary to seal the joints on the inside, because permeable joints on the cold side enable vapour to pass through and to condense on the evaporator plates. However, some argue that panels should be sealed on both sides, but that the sealant on the inner panel should be permeable.

Effective vapour control sealing ensures that a barrier, impervious to water vapour, is provided around the whole of the outside of the cold store envelope and, similarly over the warm face of any intermediate walls – for example between a cold room and a smaller freezer room section located within the same volume.

Insulated envelopes by their nature are relatively flexible structures; larger units, in particular, derive much of their strength from the support provided by external, usually steel, structures. Panel fixings and joints between panels can suffer damage through thermal movement. Panels and joints therefore need to be inspected regularly and repaired or replaced as necessary. Significant movement between walls and ceilings can occur and these areas merit close inspection.

Maintenance of the vapour control sealing on the external face of the insulation panels and pipework is essential. Warm outside air has a higher water vapour pressure than air inside a refrigerated store, and water vapour will, therefore, tends to migrate through the vapour barrier into the insulation. Water vapour penetrating the vapour barrier and passing into the insulation along joint lines can condense as water or ice, depending on the temperature within the insulation, and this will impair its insulating properties and damage the joint.

For all these reasons, when designing a cold store installation it is important that the store side of the joints should be left visible and physically accessible so that regular checks for condensation or ice formation can be made, and the cause investigated and removed. The vapour seal has a finite life, which will probably be less than the life of the insulated panels themselves. It should be repaired or replaced before it deteriorates too far. In low-temperature stores, vapour seal leaks will show as a line of snow forming on the joint line where the deterioration has occurred. Repairs should be made from the outside of the store and the snow should be removed so that the effectiveness of the leak repair can be checked.

2.4.4 Condensation control outside the cold store enclosure

Condensation on the structure and in the roof voids of the building enclosing a cold store is a recurring problem. Figure 1 highlights this risk zone. Condensation occurs when air saturated with water vapour comes into contact with cold surfaces. The amount of water vapour which air can support is a function of the air temperature. As the temperature increases, the air can contain a greater and greater amount of water vapour per unit volume.

The following enclosure surfaces are particularly prone to condensation:

- the inside of roof cladding sheets;
- the inner face of wall cladding;
- the outer face of the insulated cold store wall panels;
- the upper faces of the insulated cold store ceiling panels;
- surfaces of piped services, particularly refrigerant pipes because these are very cold;
- surfaces of cold bridges penetrating the insulated enclosure of the cold store; this includes ceiling panel suspension rods and the like;
- surfaces of structural steelwork; e.g. support brackets for pipework.

To avoid condensation, it is necessary to ventilate voids with ambient air. Approximately 10 air changes per hour are needed for ventilation of the space around a cold store. Although it is possible to achieve this with natural ventilation, mechanical ventilation is often needed, although this depends on the shape of the void. Effective ventilation ensures that the dew point in the void is identical to the dew point of the external ambient air.

Condensation on the outer cladding of the store building envelope can also occur as a result of radiation, especially on clear nights. A reduction below ambient temperature of around 4 °C may occur by this means. As the dew point is typically in the order of 2 °C below dry bulb temperature, surface condensation will occur. This can usually be avoided by insulating the building envelope.

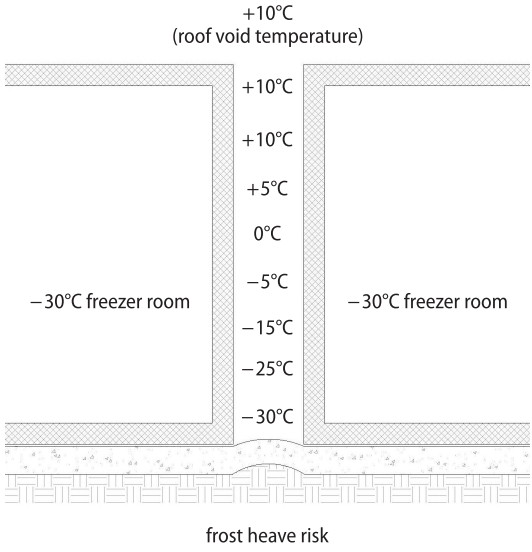
In the case of a freezer room operating at −20 °C or colder, the temperature of the ambient air immediately outside the insulated enclosure can drop below the dew point of the surrounding air, even below 0 °C; this is always a danger when there is such a large heat sink in contact with the air. This can cause condensation or ice formation on the external surface of the freezer room ceiling panels. In such circumstances, the amount of water or ice forming should be relatively small because the external relative humidity is also low. However, these accumulations need to be removed to prevent the long-term risk of panel corrosion. Safe removal requires sufficient working space, safe access and arrangements for protecting workers operating at height.

2.4.5 Frost-heave control

Frost-heave occurs when water in the subsoil beneath a continuously running freezer room freezes over time. This can occur even if the floor is insulated and the resulting expansion of the subsoil can fracture and lift the floor slab. Frost-heave is typically prevented by installing a heater mat under the freezer room floor. Ideally the mat should also extend below narrow perimeter voids outside the freezer room enclosure. Figure 3 shows the severe temperature stratification

that can occur between the roof void and floor level when two freezer rooms are placed side by side. Without good ventilation, very low temperatures may occur in the space between the rooms, leading to localized frost-heave.

Figure 3
Cross section through trapped void between freezer rooms



2.4.6 Cold store panel insulation

The recommended insulation thickness for panels with a polystyrene core is 200 mm. Polyurethane insulation is more efficient and core panels can be thinner; typically 100 to 170 mm for freezer rooms, and 100 mm for cold rooms and controlled ambient stores. A correctly specified panel insulation thickness should prevent the insulation surface temperature from falling more than 2 °C below the external air temperature, hence avoiding the dew point and resulting condensation.

2.4.7 Insulation for refrigeration pipes and other penetrations

To prevent condensation under all conditions, refrigeration pipework, electrical cables and other penetrations should be enclosed with an insulation sleeve 50–75 mm thick. These sleeves must extend for a sufficient distance beyond the cold store panel to prevent the surrounding air from cooling below the dew point. They should also be enclosed in a vapour-proof membrane to prevent condensation occurring within the insulation itself. In addition, good ventilation needs to be maintained over the surface of the sleeves.

2.4.8 Cold store maintenance schedule

Table 1 shows a suggested maintenance schedule. This can be used as a basis for developing an SOP.

Table 1
Cold store maintenance schedule

Task	Frequency
Alarm systems – heater mat	Daily
Removal of water, ice and snow from roof voids	Daily
Check operation of "trapped man" alarms	Weekly
Check operation of door seals and heaters	Weekly
Fire alarm[a]	Weekly
Check operation of emergency exits	Weekly or as required by legislation
"Walk round" inspection	Monthly
Inspection of vapour seals to ceiling panels	3-monthly
Inspection of vapour seals to wall panels	6-monthly
Mechanical installation	12 months (at least annually)
Inspection of cold store ceiling panel suspension rods and their attachments	Annually
Thermographic scan	On commissioning and every 5 years thereafter
Electrical systems	Every 5 years (ref: IEEE Code of Practice)
Professional condition survey	Every 10 years

[a] See also: Technical Supplement: *Building security and fire protection*

These intervals apply only if everything is in good order; if any defects are found then checks and essential emergency repairs should be undertaken daily.

2.5 Refrigerated vehicles

Refrigerated vehicles come in various sizes but they all comprise an insulated envelope and a cooling system. The three main types are:

- refrigerated vans
- refrigerated rigid vehicles
- refrigerated semi-trailers.

2.5.1 Refrigerated vans

Refrigerated vans may either be metal skinned delivery vans that have been modified with an insulation kit, or flatbed trucks or skeletal chassis that have had a insulated box made of glass reinforced plastic (GRP) installed. These vehicles are normally 3.5 tonnes or less. The cooling equipment is a mechanical vapour compression system using power from the van's own engine. The compressor unit is typically located in the engine bay and is driven by the fan belt. Piping links the compressor to the cooling equipment inside the insulated portion of the van. The condenser unit is located either in the engine compartment or on the roof of the vehicle. Where an electric standby system is fitted, a mains-powered compressor is installed in the condenser compartment for use when the vehicle's engine is not running. An on-board electrical lead can then be connected to a suitable single-phase mains power outlet.

The vehicle operator should carry out periodic checks to confirm the condition of the insulation and cooling equipment and to verify that the maintenance procedures laid down by the vehicle body assembler and the cooling equipment manufacturer have been carried out correctly. Maintenance procedures are defined by the equipment supplier; these procedures should be obtained from the supplier and followed carefully.

Section A1.1 of **Annex 1** details the checks for the insulated body and section A1.2 describes periodic checks that should be done on the cooling equipment for refrigerated vans.

2.5.2 Refrigerated rigid bodies

Rigid vehicles have no articulation between the cab and the insulated compartment. The vehicle is supplied as a chassis to a body builder who installs the insulated structure and the refrigeration unit; these components are produced by separate manufacturers. The refrigeration unit can be a cab overhead unit, with an independent diesel and optional electric standby mode, or an underslung electrically driven unit. The power supply for the underslung refrigeration unit can be either an alternator installed on the vehicle engine or an underslung generator. Overhead cab refrigeration units can be plugged into a normal three-phase industrial supply when the vehicle is parked.

As for refrigerated vans, the vehicle operator should carry out periodic checks to confirm the condition of the insulation and cooling equipment and to verify that the maintenance procedures laid down by the vehicle body assembler and the cooling equipment manufacturer have been followed correctly.

Maintenance procedures are defined by the equipment supplier; as noted above, these procedures should be obtained from the supplier and carefully followed.

See section A1.1 of **Annex 1** for details of the checks for the vehicle body and section A1.3 for the periodic checks to be made on the cooling equipment for rigid vehicles.

2.5.3 Refrigerated semi-trailer

A semi-trailer is an articulated independent vehicle, attached and towed by a separate tractor unit. The refrigeration unit is usually nose mounted, with an independent diesel and optional electric standby mode, or sometimes an underslung, electrically driven unit. The power for the underslung refrigeration unit is supplied from an underslung generator. Nose-mounted refrigeration units can be plugged into a normal three-phase industrial supply for standby operation.

Periodic checks should be carried out by the vehicle operator as described for refrigerated rigid vehicles. Refer also to **Annex 1**, sections A1.1 and A1.3.

2.6 Refrigerated containers

Refrigerated containers (reefer containers) are likely to be the property of a carrier or shipping company and hired for a particular voyage. Refrigerated containers also sometimes appear as static stores; these could have been purchased directly from the manufacturer, but are more likely to be older seagoing units that have been made available to the aftermarket.

Refrigerated containers destined for ocean transport will already have undergone what is known as a pre-trip inspection (PTI) by the hirer. This inspection has two stages: a visual inspection of the overall condition of the insulated structure and an automatic machinery check which is performed by a PTI function on the electronic controller. The validity of a PTI, that is the time between the PTI taking place and the ocean voyage, depends on the hirer but can be between 30 and 120 days depending on the internal policies of the shipping company. It may be possible to request copies of the condition report and the electronic download of the cooling equipment PTI report from the carrier (the shipping company). It is common practice either for the logistic service provider (LSP) or the carrier to carry out the PTI before the container is delivered to the hirer for loading. The agreed procedure should be defined in a service level agreement (SLA) between the parties to the transaction.

Anyone hiring a refrigerated container has to be aware that despite the above, according to the conditions of carriage, usually documented in the bill of lading, the onus is still on the hirers to check the condition of the equipment and that it is suitable for carriage of their goods.

Checks that should be made by the cargo owner are as follows:

- check to ensure the inside of the container is clean and free of debris;
- visual check on skin integrity covering insulation;
- check on integrity of door seals and locking mechanism;
- check on drains;
- check on fresh air setting;
- check on temperature setting.

2.7 Maintenance management

Refrigeration equipment maintenance may either be carried out in-house or outsourced to suitably qualified and certified external provider(s). In both cases it is essential to establish an institutional or contractual framework with a clearly defined SLA stating the specific maintenance standards, maintenance intervals and maximum acceptable emergency response times that are required in order to protect valuable pharmaceutical products from damage or loss.

Section 2.4 of the companion Technical Supplement *Maintenance of storage facilities* outlines the necessary framework for effective maintenance management in more detail.

2.8 Decommissioning

At the end of its economic life, fixed refrigeration equipment and refrigerated vehicles need to be decommissioned. The life of a vehicle is likely to depend on the condition of the insulated body. This in turn will depend on its use, age and the effectiveness of the maintenance programme. Cold stores, if correctly maintained, can last for more than 20 years; refrigerated vehicles are unlikely to last longer than 12 years. Refrigerators and freezers are likely to have come to the end of their life when the insulation and or door seals have deteriorated to an unacceptable condition.

The following is recommended:

a. A trained technician should remove the refrigerant from the cooling equipment. It should be incinerated in an approved plant or recycled by a refrigerant manufacturer with appropriate facilities.

b. The insulated enclosure, if it is to be used as a store, should be made safe to ensure it is impossible for people to get trapped inside.

c. If the insulation of the enclosure contains reagents with ozone depletion potential (ODP) or global warming potential (GWP), it should, if technically feasible, be crushed so that the foaming reagents can be recovered.

2.9 Staff training

All employees involved with the handling of refrigerants and the maintenance of insulated envelopes should be properly trained.

This training should cover:

a. safe handling of refrigerant fluids;
b. installation of refrigerant equipment;
c. maintenance of insulated envelopes;
d. servicing of refrigerant equipment.

Training should also sensitize staff to the adverse environmental impact of excessive energy consumption caused by poor management and poor maintenance procedures. Trainees also need to understand the damaging consequences of releasing high GWP refrigerants into the environment and, specifically, their effect in accelerating climate change.

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Annex 1

Checking refrigerated vehicles

The following checks should be carried out at least once every three years

A1.1 Checking insulation on a refrigerated vehicle

a. Examine the internal and external surfaces of the bodywork for damage, corrosion and holes. Any holes or visible insulation are unacceptable and should be plated and sealed using an appropriate sealant.
b. Check all doors and door seals. Another person should be asked to close the doors on the examiner for a few seconds; for safety reasons, ensure that the checker has a mobile phone or a third person is informed that the test is being done. Check if any daylight can be seen through the door seals; if it can, this is unacceptable and must be rectified. If the doors or their seals are damaged, repairs should be made using the correct materials.
c. Carefully check the internal front bulkhead for damage caused by handling equipment or by cargo shifting. Specifically check that the refrigerating or air distribution systems in this area are not damaged.
d. Check the fans and air distribution trunking, if fitted, for integrity and correct operation.

A1.2 Checking cooling equipment on a refrigerated van

a. Equilibrate the temperature of the inside of the van to the prevailing ambient temperature.
b. Place a temperature probe inside the vehicle in such a manner that it does not touch the floor, roof or walls.
c. Close all doors and vents and switch on the refrigeration unit, having set its thermostat to the design temperature (e.g. +2 °C to +8 °C).
d. Verify that the inside temperature of the empty equipment can be brought to the design temperature using either the electric standby or the diesel engine at high speed within a period of six hours. Both should be tested if they are independent systems.

e. Verify that the inside temperature of the empty equipment can be maintained at the design temperature for a minimum period of two hours when the engine is maintained at the idle speed set by the manufacturer (where applicable) with a tolerance of about 100 revolutions per minute. This period can be reduced to one hour if the outside temperature is higher than or equal to +30 °C.
f. Where ambient temperatures are low, verify that the design temperature can be maintained for a minimum period of two hours when the engine is maintained at the idle speed.
g. If the unit does not achieve one or more of the above, it should be sent for servicing.
h. Select defrost on the controller and check that the unit terminates the defrost cycle and returns to refrigeration. Check that the air circulation stops during defrosting.
i. Again at low ambient temperatures, select a temperature setting with the thermostat between 0 °C and +5 °C, and check that the refrigeration unit heats and will control at the selected temperature.

Provided that the outcomes of the above checks are satisfactory then the unit can be approved as satisfactory for a further period in service.

A1.3 Checking cooling equipment on a rigid vehicle or semi- trailer

a. Equilibrate the temperature of the inside of the trailer to the prevailing ambient temperature.
b. Place a temperature probe inside the vehicle in such a manner that it does not touch the floor, roof or walls.
c. Close all doors and vents and switch on the refrigeration unit, having set its thermostat to 5 °C below the design temperature (e.g. +2 °C to +8 °C).
d. Verify that the inside temperature of the empty equipment can be brought to the design temperature within a maximum period (in minutes), as prescribed in Table A1.1.

Table A1.1
Maximum period within which temperature of the empty equipment is to be brought to the design temperature (in minutes)

Ambient °C[a]	30	29	28	27	26	25	24	23	22	21	20	19	18	17	16	15
Chilled 2–8 °C	360	350	340	330	320	310	300	290	280	270	260	250	240	230	220	210
Frozen −20 °C	180	173	166	159	152	145	138	131	124	117	110	103	96	89	82	75

[a] If the ambient temperature is lower than 15 °C take the minimum time period, if higher than 30 °C take the maximum period.

e. If the unit does not achieve the prescribed temperature change, the unit should be serviced.
f. Select defrost on the controller and check that the unit terminates the defrost cycle and returns to refrigeration. During the defrost, check that the air circulation stops. Nose-mounted units usually have a damper which shuts off the airflow during defrost.
g. Select a temperature setting with the thermostat between 0 °C and +5 °C, and check that the refrigeration unit heats and will control at the selected temperature.

Provided that the outcomes of the above checks are satisfactory then the unit can be approved as satisfactory for a further period in service.

Revision history

Date	Change summary	Reason for change	Approved

Supplement 10

Checking the accuracy of temperature control and monitoring devices

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

Annex 9: Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products

May 2015

Contents

Abbreviations

DUT	device under test
SOP	standard operating procedure
TTSPP	time- and temperature-sensitive pharmaceutical product

Acknowledgements

The author of this document is Claude Hafner of Berlinger & Co. AG, Switzerland.

Glossary

Standard operating procedure (SOP): A set of instructions having the force of a directive, covering those features of operations that lend themselves to a definite or standardized procedure without loss of effectiveness. Standard operating policies and procedures can be effective catalysts to drive performance improvement and improve organizational results.

Temperature control device: A device which actively controls the operation of cooling plant used to store or transport TTSPPs.

Temperature monitoring device: A device which monitors the temperature of spaces used to store or transport TTSPPs.

Thermal time constant: The most common definitions of the thermal reaction time are the so-called tau (τ, the 19th letter of the Greek alphabet) and "T90". Tau stands for the time a device needs to adapt to 63% of the end value of a temperature change whereas T90 represents the time to adapt to 90% of the change. T90 is approximately equal to 2.5 times Tau. These constants are commonly evaluated by experiment on the test device under well-defined conditions as described in EN 12830.[1]

Time and temperature-sensitive pharmaceutical product (TTSPP): Any pharmaceutical good or product which, when not stored or transported within predefined environmental conditions and/or within predefined time limits, is degraded to the extent that it no longer performs as originally intended.

Triple point: The temperature and pressure at which a substance can exist in equilibrium in the liquid, solid, and gaseous states. The triple point of pure water is at 0.01 degrees Celsius and 4.58 millimetres of mercury and is used to calibrate thermometers.

[1] EN 12830, Temperature recorders for the transport, storage and distribution of chilled, frozen, deep-frozen/quick-frozen food and ice cream – Tests, performance, suitability.

1. Introduction

This technical supplement has been written to amplify the recommendations given in section 4.10 of WHO Technical Report Series No. 961, 2011, Annex 9: *Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products*.[2] It describes a way to check the accuracy of temperature monitoring and temperature control devices using the "ice-water" procedure, and it outlines the limitations of this approach. This method can be used in situations where it is not possible to carry out a full three-point calibration using the services of a nationally or internationally accredited calibration laboratory.

1.1 Requirements

As a general rule, temperature measurement and control devices must periodically be calibrated to prove their accuracy over the full operating temperature range and according to the device's data sheet definitions. Proven accuracy is mandatory because inaccurate readings can lead to a false sense of security and place time- and temperature-sensitive pharmaceutical products (TTSPPs) at risk.

Some devices are covered by calibration certificates from the device manufacturer. These certificates are valid for a defined period and the associated devices may be used throughout this period without additional calibration. An example of this is a single-use temperature monitoring device, which is designed to be discarded at the end of a journey, or when the battery powering the device expires. To ensure conformity, the manufacturer of such products must supply a calibration certificate with the device.

However, there are circumstances under which proper device calibration or recalibration is needed. The list below is not comprehensive but illustrates some of these circumstances:

- A calibration certificate is not available because it has been lost.
- The device is used for longer than the period covered by the calibration certificate, either at the user's risk or with the approval of the manufacturer.
- The device was used or treated beyond the manufacturer's data sheet limitations (e.g. it was subjected to excessive temperature or shock).
- The battery powering the device was replaced.
- The device's measurements are suspect.
- The device manufacturer specifies that a calibration procedure should be carried out at regular intervals.

[2] http://apps.who.int/medicinedocs/documents/s18683en/s18683en.pdf

- Regulatory bodies require regular proof of calibration, e.g. at 12-month intervals, and proof of calibration cannot be provided by the manufacturer's certificate.

1.2 Objectives

Wherever possible, calibration should be carried out in accordance with the device manufacturer's instructions, or by following a device-specific standard operating procedure (SOP). Ideally, a full three-point calibration should be carried out by a nationally or internationally accredited calibration laboratory with proven accuracy standards and appropriate equipment. However, there are many circumstances where accredited calibration is not possible because no suitable laboratory is available. The simple and accurate method described in this Technical Supplement can be used to prove the device's functionality and accuracy at one single point of temperature using the so-called ice-water procedure.

1.3 Target readership

This document is intended to be read by managers and technical staff who are responsible for the monitoring, installation and maintenance of temperature measurement and control equipment throughout the cold chain. Responsible managers must understand the necessity for calibration; in the absence of a suitable calibration laboratory, technical personnel must be able to carry out and/or supervise the accuracy checking procedure described below.

2. Guidance

The method described below is relatively simple to carry out but requires close attention to detail. The accuracy of the results is also dependent upon the use of a high-quality reference thermometer with a valid calibration certificate.

2.1 Associated materials and equipment

Reliable results will be achieved if the following equipment and materials are used.

a. Wherever possible, use reference temperature measurement equipment regularly calibrated by an accredited laboratory, e.g. Fluke Hart Scientific precision equipment.[3] Figure 1 shows an example of this type of instrument.

Figure 1
Example of a reference thermometer

Source: Fluke Hart

b. Always use a temperature measurement reference instrument which is of higher accuracy than the device to be checked – for example, a thermometer with a rated accuracy of ±0.2 °C should be used to check a device with a rated accuracy of ±0.3 °C.

[3] http://us.flukecal.com/products/temperature-calibration
Note that mention of this company does not imply any endorsement or recommendation by the World Health Organization.

c. A thermally insulated container, tub open to the atmosphere, and sufficiently large to contain enough melting ice-water to provide stable temperature conditions and allow full immersion of the device under test (DUT) as described in section 3. In the cold chain operating environment, a vaccine carrier or small cold box with a hinged or separate lid would be a suitable choice. The size required depends on the dimensions of the DUT.
d. Disposable latex gloves.
e. Enough clean distilled water must be available to make ice cubes and to set up a proper and stable ice-water triple-point mixture. The DUT should be sealed inside a transparent waterproof pouch before immersing it in the liquid in order to avoid water ingress and resulting damage. As much air as possible should be extracted to ensure that the DUT is in good contact with the ice-water mixture. Sealing is always recommended, even for DUTs with a high international protection rating (IEC 60529 IP protection class rating), because the protection might have been damaged – for example by dropping the device or during battery replacement. Where the DUT has an external sensor, the sensor may be immersed directly in the bath, provided it has an IP7 or IP8 protection class rating. Otherwise it should be sealed in a pouch as described above, with the pouch tied tightly around the lead above the level of the ice-water.

2.2 Procedure

The ice-water bath provides an accurate reference temperature at 0.0 °C if the melting ice-water mixture is properly set up, handled and maintained. An accurate temperature is achieved by this method because an ice-water mixture in a container which is open to the atmosphere will stabilize at its own "triple point". At this point all three aggregate states of water coexist: liquid, solid and gaseous. For more physical details refer to ASTM E563-11.

2.2.1 Prerequisites

a. Only place clean equipment and distilled water inside the container. Use clean latex gloves to handle ice and equipment.
b. Although the temperature of the ice-water mixture stabilizes itself, its temperature must still be monitored before and during the procedure using the calibrated reference thermometer. This is a mandatory requirement in order to prove the functionality and stability of the ice-water bath.

c. During extended testing periods enough ice must be added to the bath to maintain the water–ice equilibrium temperature and to prevent a possible temperature rise caused by excessive melting of the ice.

d. Note that only DUTs which display a temperature reading can be checked by this method because the temperature indicated by the DUT must be compared to the ice-water bath temperature. Devices without a display need additional equipment to capture an immediate measurement read-out so that this can be compared with the reference temperature reading. This additional equipment is manufacturer-specific.

2.2.2 Establishing the ice-point bath (excerpt from ASTM E563-114[4])

a. Before using the bath, chill the required amount of distilled water close to 0.0 °C.

b. Freeze a suitable amount of the same water to produce ice-cubes, making sure that there is a sufficient quantity for the complete test run.

c. Prepare shaved or fine crushed ice with a maximum 2 mm to 3 mm particle diameter; the finer the ice particles, the more accurate the ice-water temperature.

d. Prepare the bath in the clean thermally insulated container. The container should be large enough not to affect the water-ice equilibrium temperature. The width, length or diameter and the overall depth must ensure that, when the thermal equilibrium state is reached, the test objects will not significantly modify the temperature of the bath over the region to which the ice point is to be applied. For normal applications, a width, length or diameter at least 100 mm larger than the maximum DUT dimension size, and a depth of at least 300 mm should be sufficient.

e. Alternately add shaved ice and chilled water to the vessel, using just enough water to saturate the ice but not enough to float it. As the vessel fills, compress the ice-water mixture to force out excess water. The objective is to surround each particle of ice with water, filling all voids, but to keep the ice particles as close together as possible.

[4] ASTM E563-11 Standard practice for preparation and use of an ice-point bath as a reference temperature. West Conshohocken, PA: ASTM.

Continue adding ice and water and compressing until the vessel is filled to the required level. Decant or siphon off excess water.

f. Use the reference thermometer throughout the entire test period to confirm that a stable temperature is maintained.

g. Cover the ice-point bath to protect it during the test period. Use an opaque and thermally insulating cover or stopper that is suitable for the application. This reduces heat transfer to the ambient environment through the surface of the bath. Allow the bath and vessel to equilibrate for at least 30 minutes before using.

2.2.3 Placing the device in the bath

a. Seal the DUT in a clean plastic bag. Make sure that as little air as possible is trapped inside the bag in order to avoid false results caused by floating and/or lack of contact between the DUT and the ice-water.

b. Pre-cool the DUT in water at less than +3.0 °C before immersing it in the bath. Pre-cooling the DUT reduces the time taken to reach equilibrium at the ice point; it also helps to preserve the bath at the ice point for a prolonged time. Furthermore, it ensures that the water–ice interface will be in close contact with the DUT; negligible melting is important, otherwise the water film thickness between the DUT and the ice-water will increase and distort the test results.

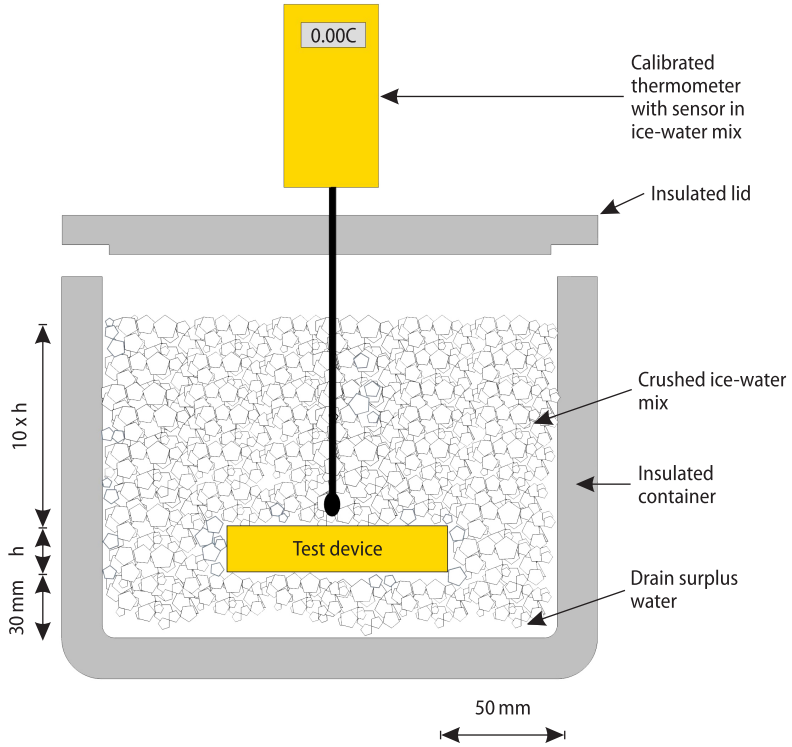
c. Form a well in the ice-water bath that has the dimensions and intended immersion depth of the DUT.

d. Insert the sealed DUT to a depth of at least ten object diameters or heights respectively below the surface. Keep the DUT a minimum of 30 mm above the bottom of the container to avoid the zone at the bottom where denser meltwater tends to accumulate (Figure 2).

e. Replace the lid. For devices with an external sensor, make sure that the lid seals well around the sensor lead.

f. Allow the bath and DUT to come to thermal equilibrium. Allow for the thermal time constant of the DUT.

Figure 2
Ice-water bath arrangement



2.2.4 Carrying out the accuracy check, step-by-step

a. Establish and maintain the ice-water bath, prove its temperature with the reference thermometer.
b. Ensure that the DUT remains immersed in the ice-water bath as described in point 3.3d above.
c. Directly read the DUT temperature display while it is still immersed in the bath. If this is not possible, remove the DUT and immediately read its temperature indicator; prompt action avoids false readings resulting from exposure to the ambient temperature.
d. Record the readings on an accuracy check reference data chart as per sample taken from EVM-SOP-E2-2. Store the chart at least until the next accuracy check takes place, and preferably for a minimum of three years.

2.2.5 Maintaining the bath temperature

a. As ice particles in the bath melt, excess water begins to accumulate. This melt water has a temperature slightly above 0.0 °C. Since the density of water is at its maximum at +4.0 °C, the slightly warm meltwater will collect at the bottom of the bath and, hence, around the DUT. Under these conditions, the bath will no longer be at 0.0 °C and cannot serve as an ice-point bath. For this reason surplus water should be removed, as it accumulates, from the bottom of the bath by decanting or siphoning. The presence of excess water can be detected if water overspill occurs when the ice is depressed. Add ice particles, and chilled water, as necessary so that the ice slush column always extends to at least 30 mm below the lowest point of the test object.
b. In order to sustain the ice-point over prolonged periods, the ice-point bath can be immersed in another larger insulated bath that is kept near to 0.0 °C.

2.2.6 Actions to take following the test

There are two possible test outcomes: pass or fail.

1. The DUT passes the test

A pass is achieved if the DUT temperature indication deviates from the reference thermometer reading[5] by less than the tolerance allowed in the data sheet. In this case the DUT should be physically labelled as follows:

> *Accuracy valid until:* <enter the date one year after the accuracy check>.
> *Note:* If the manufacturer or the regulatory authority stipulates a shorter or longer period of validity, enter the appropriate date to take account of this.

After this period expires the accuracy check must be repeated, as described in this document.

[5] For example, if the reference instrument has an accuracy of ±0.5 °C and the DUT deviates 0.3 °C from the reference instrument reading, this is a pass.

2. The DUT fails the test

If the DUT temperature indication deviates from the reference thermometer reading[6] by more than the tolerance allowed in the data sheet the DUT fails the test. In this case, take one if the following actions:

a. If the sensor can be adjusted, carry out the adjustment according to the manufacturer's instructions. Then repeat the accuracy check according to the procedure described above.
b. If the sensor can be replaced, but the accuracy of the device is not solely dependent on the performance of the sensor head, replace the sensor according to the manufacturer's instructions. Then repeat the accuracy check.
c. If the sensor can be replaced, and the accuracy of the device depends entirely on the performance of the sensor head, the sensor can simply be replaced with a new factory-calibrated sensor in accordance with the manufacturer's instructions. No further check is then required until the next accuracy/calibration date falls due.
d. If the sensor can neither be replaced nor adjusted, the whole DUT must be replaced and a *non-conformity report* must be issued to the relevant decision-makers to ensure that the DUT is removed from service and replaced.

[6] For example, if the reference instrument has an accuracy of ±0.5 °C and the DUT deviates 0.6 °C from the reference instrument reading, this is a failure.

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Annex 1

Generic temperature accuracy check form

Store location: _____

Form start date: _____

Form finish date: _____

Date	Device description	Device location	Reference thermometer	Check method	Reference temperature	Difference from reference	Initials	Comments	Verified by/date
12 Dec 2013	DUT #12341234	Cold room # 1	XYZ 500	Water-ice bath	0.0 °C	+0.2 °C	UK	checked - OK	SJ 15 Dec2013

Revision history

Date	Change summary	Reason for change	Approved

Supplement 11

Qualification of refrigerated road vehicles

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

Annex 9: Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products

May 2015

Contents

Abbreviations

±K	Difference in absolute temperature
ATP	Agreement on the International Carriage of Perishable Foodstuffs and on the Special Equipment to be Used for such Carriage
cGMP	current good manufacturing practice
EDLM	electronic data logging monitor
EN	European norm (standard)
IQ	installation qualification
OQ	operational qualification
PQ	performance qualification
SOP	standard operating procedure
TTSPP	time- and temperature-sensitive pharmaceutical product

Acknowledgements

The author of this document is Richard Lawton, Technical Director, Cambridge Refrigeration Technology, Cambridge, England.

Glossary

Electronic data logging monitor (EDLM): A small portable device that measures and stores temperature at predetermined time intervals by means of an electronic sensor. They have programmable alarm capabilities, integrated displays, and can create reports and graphs which may be permanently stored, shared and analysed via proprietary hardware, software, desktop application or through hosted databases.

Coefficient of heat transfer (The "U" value, also referred to as the "K" coefficient in the ATP Agreement): The overall heat transfer of the equipment, defined as the heating power or cooling capacity, W, per degree temperature difference, T, between the internal and external surfaces over the surface of the body, S.

The units are $W/(m^2K)$ and its formula is below.

$$K = \frac{W}{Sx\Delta T}$$

Installation qualification (IQ): The process of obtaining and documenting evidence that the premises, equipment and supporting systems have been provided and installed in compliance with their design specifications.

Operational qualification (OQ): The process of obtaining and documenting evidence, under controlled conditions, that the premises, equipment and supporting systems operate in accordance with their design specifications.

Performance qualification (PQ): The process of obtaining and documenting evidence that the premises, equipment and supporting systems, as connected together, will consistently perform in accordance with the approved process method and specifications.

Pharmaceutical product: Any product intended for human use or veterinary product intended for administration to food producing animals, presented in its finished dosage form, that is subject to control by pharmaceutical legislation in either the exporting or the importing state and includes products for which a prescription is required, products which may be sold to patients without a prescription, biologicals and vaccines. Medical devices are not included.[1]

[1] Definition from WHO/QAS/08.252 Rev 1 Sept 2009. *Proposal for revision of WHO good distribution practices for pharmaceutical products – Draft for comments.*

Qualification: Documented testing that demonstrates with a high degree of assurance that a specific process will meet its predetermined acceptance criteria.[2]

Refrigerated vehicle: Road transport vehicle such as a van, truck or semi-trailer whose isolated thermostatically controlled cargo compartment is maintained at a temperature different (lower or higher) than the external ambient conditions. The environment inside the cargo compartment may be *temperature-controlled* or *temperature-modified*.

Standard operating procedure (SOP): A set of instructions having the force of a directive, covering those features of operations that lend themselves to a definite or standardized procedure without loss of effectiveness. Standard operating policies and procedures can be effective catalysts to drive performance improvement and improve organizational results.

Temperature-controlled: Includes any environment in which the temperature is actively or passively controlled at a level different from that of the surrounding environment within precise predefined limits.

Temperature-modified: Includes any environment in which the temperature is predictably maintained at a level different from that of the surrounding environment, but is not actively or passively controlled within precise predefined limits.

Time and temperature-sensitive pharmaceutical product (TTSPP): Any pharmaceutical good or product which, when not stored or transported within predefined environmental conditions and/or within predefined time limits, is degraded to the extent that it no longer performs as originally intended.

Validation: Documented testing performed under highly controlled conditions, demonstrating that processes, methods, and systems consistently produce results meeting predetermined acceptance criteria.[3]

[2] Definition from Parenteral Drug Association (PDA) Technical Report No. 39: Guidance for temperature controlled medicinal products: maintaining the quality of temperature-sensitive medicinal products through the transportation environment. Bethesda (MD): Parenteral Drug Association; 2007.

[3] Parenteral Drug Association (PDA) Technical Report No. 39: Guidance for temperature controlled medicinal products: maintaining the quality of temperature-sensitive medicinal products through the transportation environment. Bethesda (MD): Parenteral Drug Association; 2007.

1. Introduction

This technical supplement has been written to amplify the recommendations given in WHO Technical Report Series No. 961, 2011, Annex 9: Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products.[4] It outlines the actions that need to be taken to qualify refrigerated vehicles equipped with active temperature-control systems which are used to transport TTSPPs. Related topics are covered in the following Technical Supplements:

- *Checking the accuracy of temperature control and monitoring devices*
- *Refrigeration equipment maintenance*
- *Transport route profiling qualification*

What is qualification?

In the context of this series of Technical Supplements, *qualification* is an inspection and testing process used to establish that a piece of equipment or a physical installation is fit for purpose in the operational context within which it will be used. There are typically three stages in the process. Each stage must be fully completed before the next one begins.

Stage 1 (for equipment): Establish by laboratory testing under tightly controlled conditions that a specific item of equipment performs in accordance with the user requirements specification (URS). This is design qualification. Although *design qualification* demonstrates compliance with the URS and associated test protocols, it does not prove that the equipment will be suitable in a specific operating environment because the URS and the test procedures are unlikely to reflect the full range of operating conditions.

Stage 1 (for installations): Establish by documented inspection and testing that an installation[5] that has been assembled in a specific location is fully in accordance with the URS and installation drawings. This is *installation qualification*.

Stage 2: Establish by further documented testing under controlled conditions that this equipment or installation is likely to perform as intended in the operating environment in which it will be used. This is *operational qualification*.

[4] http://apps.who.int/medicinedocs/documents/s18683en/s18683en.pdf

[5] The installation will typically incorporate components that have a design qualification.

Stage 3: Carry out a final stage of documented testing to establish with a high degree of assurance that the equipment or installation, together with all associated systems, does indeed perform as intended under routine operating conditions. This is *performance qualification*.

1.1 Requirements

Where refrigerated vehicles are directly owned and/or operated it is important, wherever possible, to qualify each vehicle before it becomes operational. In addition, where a contract carrier service is used, the shipper has a duty to ensure that the carrier's vehicles are appropriately qualified. The qualification procedure should:

- **Demonstrate** that the temperature distribution within the payload area of the temperature-controlled compartment is maintained within the range specified for the products being transported (e.g. +2.0 °C to +8.0 °C). The qualification procedure must be able to assess actual product temperatures for commonly used load layouts. Qualification should be carried out at the ambient temperature extremes anticipated during normal operation, over known distribution routes.
- **Define** zones within the vehicle's payload area that 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 or minimum in the event that the temperature-controlling unit fails. Similar tests should be used to validate the anticipated door-opening times that will occur during deliveries.
- **Document** the qualification exercise for internal quality assurance and external regulatory purposes.

This procedure constitutes a temperature-mapping exercise similar to that employed for fixed temperature-controlled storage facilities.

An alternative approach is to perform an initial full qualification on each trailer/ temperature-control 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 monitoring shows unexplained variability that is greater than normal.

These requirements are to ensure that TTSPPs can be safely transported within the transport temperature profile defined for each product and that

compliance can be demonstrated to the regulatory authorities and other interested parties.

1.2 Objectives

The objective of this Technical Supplement is to provide guidance on how to qualify refrigerated vehicles used for transporting TTSPPs in a way which meets the above requirements.

1.2.1 Verification

When a refrigerated vehicle is procured, the purchaser must exercise due diligence to ensure that the required performance and detailed characteristics are clearly specified so that the vehicle supplier can provide equipment that matches the needs of the operating environment. Only equipment which has been properly *verified* against industry standards and norms should be considered. If procurement is done correctly there is a high probability that the vehicle will perform well in the operating environment.

1.2.2 Qualification

Once the vehicle has been delivered it is essential that its actual performance is *qualified*. Qualification 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.

Qualification procedures are increasingly being seen as a requirement of current good manufacturing practice (cGMP). The qualification 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 the equipment concerned with maintaining and ensuring product quality operates 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.

1.3 Target readership

The target readership is the owners and operators of refrigerated vehicles used to transport TTSPPs, the aim being to provide sufficient information to enable them to produce a standard operating procedure (SOP) relevant to their own specific transport operations.

2. Guidance

The importance and regulatory significance of verification, validation and qualification has been outlined above. This section describes the principal steps that need to be taken to achieve these objectives.

2.1 Associated materials and equipment

The following are required:

- A sufficient quantity of electronic data logging monitors (EDLMs), qualified to European Norm (EN) 12830:1999, together with the necessary download software. WHO Performance, Quality and Safety (PQS) prequalified EDLMs may be used for this purpose.[6]
- Where possible, an ATP-approved temperature-controlled chamber should be used. The specific requirements of the cold chain for pharmaceutical products have not been ratified, but recommended guidelines have been produced.[7]
- Real, expired or dummy product.

2.2 Preliminary construction validation

The following checks should be carried out to satisfy the requirements at the IQ stage. Essentially this is an inspection procedure designed to ensure that the vehicle meets required standards; these requirements should have been stated clearly in the procurement specification.

2.2.1 Temperature-controlling equipment

The ATP agreement stipulates that refrigeration equipment should have an over-capacity of a least 1.75 times the overall heat ingress into the insulated body under operating conditions at an ambient temperature of +30.0 °C. If the predicted ambient temperature is above +30.0 °C, it would be prudent to increase the over-capacity to 2.25. In cold climates, heating capacity will also be required to provide low temperature protection if the temperature-controlled compartment needs to be maintained above 0.0 °C.

[6] See: http://apps.who.int/immunization_standards/vaccine_quality/pqs_catalogue/categorypage.aspx?id_cat=35

[7] Association Francaise du Froid. Practical guidelines – cold chain for medicines. Paris: Association Francaise du Froid; 2009.

2.2.2 Thermal insulation

ATP regulations state that for frozen transport the thermal insulation of the refrigerated compartment should have a K-coefficient of heat transfer of ≤ 0.4 W/m²K, and for chilled transport a value of ≤ 0.7 W/m²K. It is recommended that all new vehicles be selected with an insulation coefficient < 0.4 W/m²K.

2.2.3 Performance checks

Before qualification, the performance of the temperature-control and the thermal insulation should be checked according to the maintenance procedure; see the companion WHO Technical Supplement: *Refrigeration equipment maintenance*.

2.3 Field shipment test

The field shipment test is designed to satisfy parts of the operational qualification (OQ) and performance qualification (PQ) stages.

2.3.1 Purpose

The purpose of this test is to demonstrate whether the product temperature distribution within the temperature-controlled compartment is maintained within the specified limits. Testing should be designed to cover commonly used load layouts at the ambient temperature extremes anticipated during normal operation over known routes.

Ideally a temperature-controlled chamber would be used for the test because this provides a consistent, monitored environment. A disadvantage of this approach is the validity of the simulated conditions; it may be difficult accurately to predict the real-world conditions of a delivery.

In most cases, a large test chamber will not be available. However, a static test at ambient temperatures may still be appropriate for an OQ.

2.3.2 Loading

When conducting a field shipment test under real operating conditions, there are two options:

- *Use real products:* In the case of a simultaneous transport and validation exercise, use actual products.
- *Use expired or dummy products:* If validation is being carried out before live operations commence, use real products that have reached their expiry date whenever possible. Otherwise use substitutes that have similar thermal properties, mass and packaging to the actual products to be transported.

Note: If expired product is shipped between countries, pay special attention to customs and security restrictions and requirements.

The vehicle should be packed according to the manufacturer's instructions and should reflect the load layout commonly used. Although the precise equipment and layout will depend on the vehicle and the products transported, general guidance can be found in the WHO guidance on *Loading and operating refrigerated vehicles*.[8]

2.3.3 Temperature probe placement

Temperature probes should be fixed within the packaging of the transported products. Ideally the temperature probes should be spread throughout the load; however, as a minimum requirement, they should be placed in the locations most vulnerable to temperature excursions. It is also informative to include less vulnerable positions (see **Annex 1**). To identify these "worst case" positions, an initial temperature mapping of the refrigerated compartment should be carried out *before* the qualification exercise. This helps ensure that vulnerable points are covered by temperature probes during qualification.

If there are multiple drop-off points along the delivery route, this should be considered when locating the temperature probes. At least two probes covering the hottest and coldest locations in the load compartment must remain attached to the payload up to the final drop-off.

2.3.4 Test procedure

A static temperature mapping exercise is recommended before conducting the mobile qualification tests. This will establish worst case positions (e.g. the hottest and coldest spots in the load compartment). These positions can be used as locations for EDLMs during the mobile tests.

As a minimum, a series of four tests should be conducted to reflect the full range of the vehicle's use.

a. test performance with maximum payload during the warmest season;
b. test performance with minimum payload during the warmest season;
c. test performance with maximum payload during the coldest season;
d. test performance with minimum payload during the coldest season.

The operator may wish to repeat these tests for statistical confirmation. See the companion Technical Supplement: *Transport route profiling qualification*.

[8] World Health Organization. EVM SOP E7-05 Loading and operating refrigerated vehicles. Geneva: WHO Effective Vaccine Management (EVM) Initiative; 2011 (http://www.who.int/immunization/programmes_systems/supply_chain/evm/en/index2.html, accessed 10 February 2015).

During the tests, the vehicle should be operated as intended and the route should be chosen to reflect a typical worst-case scenario. The tests should preferably be conducted during an actual delivery in order to collect accurate data. If this is not possible, a representative route should be chosen. A worst-case scenario would usually include multiple drop-offs with associated door openings, with the shortest journey time between drop-offs, and overnight stops on electric standby.

Following the completion of each test, the data from the loggers can be downloaded to determine the overall performance.

Note: The need to perform warm-season and cold-season testing, as described above, means that the vehicle cannot be fully qualified until both seasons have passed, which may be as long as six months. Therefore the vehicle can only be *provisionally* qualified after completion of the first two tests. The second pair of tests must be completed satisfactorily before the vehicle is *fully* qualified for use throughout the year. If a test chamber is available, the tests for the two seasons can be simulated during a static temperature-mapping exercise, as can the effect of multiple drop-offs and overnight stops.

2.3.5 Acceptance criteria

In order to pass the OQ and PQ, the product temperatures should remain within the required temperature range during the entire route and across all four tests. For example, if the requirement is for +2.0 °C to +8.0 °C, the minimum temperature recorded should not be below +2.0 °C, −0.5 °C and the maximum should not exceed +8.0 °C, +0.5 °C.[9]

2.4 Temperature-control failure test

A temperature-control failure test is required to complete the OQ and PQ. This test determines the time in which a breakdown becomes critical.

2.4.1 Purpose

The purpose of the test is to demonstrate the time taken for temperatures to exceed the designated maximum or minimum in the event that the temperature-controlling unit fails. Note that this test cannot be carried out using real products

[9] WHO PQS specifications require EDLM devices to have an accuracy of ±0.5 °C.

during a simultaneous transport and validation test because the product would be damaged. For this reason a simulated load is recommended.

2.4.2 Loading

Do NOT use real product for this test as it will be irrevocably damaged. Instead use expired product if this is available and has been subjected to a thorough risk assessment – it is essential that expired products do not reach the market in the event of theft or mismanagement at the destination point. Alternatively, use a substitute with similar thermal properties, mass and packaging to the actual products. The chosen substitute must be suitable for the test route; for example, if a border crossing is involved, the product should be selected to avoid problems with customs. The final option is to use empty boxes which represent typical packaging type(s); this option simulates the worst case (lowest) thermal mass situation. In all cases minimal payload should be used as shown in **Annex 1**, Figure A1.1.

Again the vehicle should be packed according to the manufacturer's instructions and should reflect the load layout commonly used. Tests should be undertaken in ambient conditions reflecting the extremes of both heat and cold likely to be encountered during service.

2.4.3 Temperature probe placement

Temperature probes should be fixed within the packaging of the products being transported to ensure that the temperature of the product itself is recorded and not that of the surrounding air; air temperature within the load compartment may fluctuate outside the designated range for short periods while the product temperatures remain unchanged.

Ideally the temperature probes should be spread throughout the load; however, as a minimum requirement they should be placed in the locations most vulnerable to temperature excursion. It is also informative to include less vulnerable positions. See **Annex 1**.

2.4.4 Test procedure

The temperature-control system should be set to control the product temperatures within the standard operating temperature range. Before loading begins, make sure that the load compartment has been preconditioned to the designated temperature and check to confirm that the system has reached the set point temperature. Generally, the mid-point of the temperature range should be chosen to stabilize the products while allowing for some variation in the product temperatures. For example, if the product requires temperatures from +2.0 °C to +8.0 °C, select a set point of +5.0 °C. The system should be left to allow the

products to stabilize. The time needed for this will vary for different types of insulated equipment, although approximately 12 hours should be sufficient. A temperature sensor with a remote hand-held monitor could be attached to product nearest the doors to allow for temperature readings to be taken during the test, thereby assisting in monitoring the progress of the test.

Once stabilization is achieved, the temperature-control system should be switched off. Temperature readings can be taken periodically to provide a guide to the internal temperature. The test is complete when a single product temperature exceeds the specified maximum or minimum for the designated operating temperature classification. Following the test, the data from the loggers can be downloaded to determine the overall performance.

2.4.5 Acceptance criteria

The time taken for the product temperatures to exceed the intended maximum or minimum should be recorded in the OQ with reference to the unit being tested. These data can be used to help define contingency procedures and required response times during a transport emergency.[10]

2.5 Documentation

Comprehensive documentation is an essential part of the qualification process because it enables the long-term performance of the vehicle fleet to be monitored and it allows the operator and regulatory bodies to demonstrate compliance with good practice.

2.5.1 Designation of the vehicle

The insulated body and the associated temperature-control unit should both be uniquely identifiable. This is achieved by recording the data on the manufacturer's plate(s), which must clearly and indelibly show at least the following particulars:

- country of manufacture;
- name of manufacturer;
- model;
- serial number;
- year and month of manufacture.

[10] See: EVM-SOP-E7-06: Responding to emergencies during vaccine transport operations.

2.5.2 Results of the qualification

Appropriate documentation must be kept to ensure that there is a historical record of OQ and PQ qualification for a particular insulated body. All qualification results should be recorded, together with a list of any subsequent modifications. Instances of unexplained performance variability should be recorded; these records should be made available for future qualifications, or when there is a change of operator.

2.6 Vehicle qualification failure

In the event that a vehicle fails to meet the standard for qualification, a recommendation should be made, highlighting the reasons for the failure and any action that could be taken to improve the performance of the vehicle.

Qualification records should be stored as usual together with any recommendations or modifications made.

2.7 Calibration

The EDLMs used for qualification, as well as any on-board temperature monitoring equipment, should be recalibrated according to the procedure and time frame specified by the manufacturer, e.g. EN 13486:2003. EDLMs with non-replaceable batteries are supplied with a valid calibration certificate from the logger manufacturer; these devices do not need to be recalibrated.

If a temperature-monitoring device fails the calibration, it should be clearly marked and removed from service to be repaired or disposed of.

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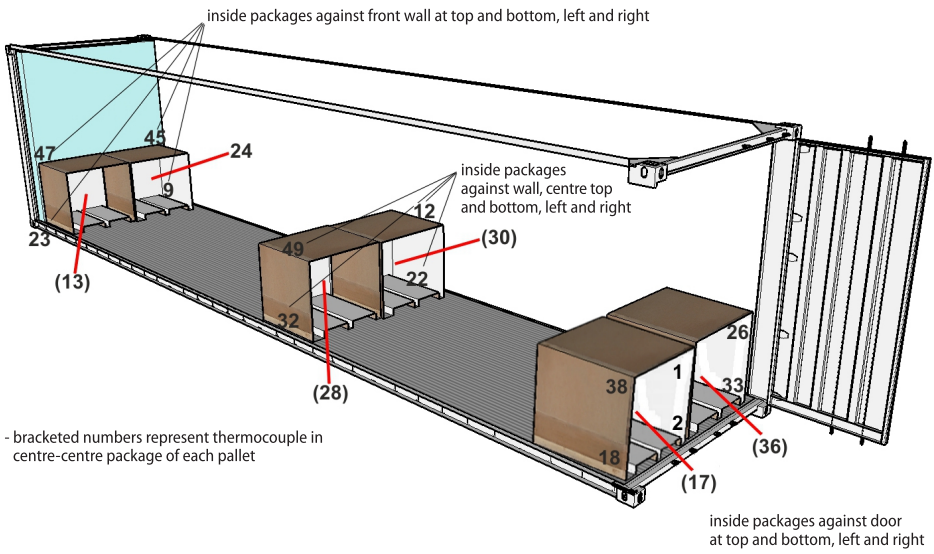
Annex 1

Placing electronic data logging monitors or temperature sensors

Electronic data logging monitors (EDLMs) and/or their sensors should be placed as shown in Figure A1.1. The minimum recording requirements for qualification testing are:

- outside ambient temperatures around the external surfaces;
- air delivery of the refrigeration unit;
- air return of the refrigeration unit;
- product close to the delivery air of the refrigeration unit;
- product in any areas likely to be deprived of airflow;
- product close to the walls;
- product close to the door.

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



Source: Cambridge Refrigeration Technologies

Note: If it is intended to double-stack pallets it is essential to validate this arrangement during the qualification process.

Revision history

Date	Change summary	Reason for change	Approved

Supplement 12

Temperature-controlled transport operations by road and by air

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

Annex 9: Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products

May 2015

Contents

Abbreviations

AWB	air waybill
CI	chemical indicator
CCP	critical control point
CRT	controlled room temperature
ETI	electronic temperature integrator
EDLM	electronic data logging monitor
IATA	International Air Transport Association
NOTOC	notification to captain
PDA	Parenteral Drug Association
SLA	service level agreement
SOP	standard operating procedure
TTI	time–temperature integrator
TTSPP	time- and temperature-sensitive pharmaceutical product
ULD	unit load device
URS	user requirements specification

Acknowledgements

The authors of this document are Kevin O'Donnell, Exelsius Cold Chain Management Consultancy and member of the United States Pharmacopeia Expert Committee of Packaging, Storage and Distribution 2010–2015 cycle and Jim Bacon, Senior Director, Demand Planning and International Customer Operations – US Office, Grifols, Inc.

Glossary

3PL: Third-party logistics provider: a firm that provides service to its customers of outsourced (or "third party") logistics services for part, or all of their supply chain management functions.

4PL: Fourth-party logistics provider: a general contractor who manages other 3PLs, truckers, forwarders, custom house agents, and others, essentially taking responsibility for a complete logistics process for the customer.

Active systems: Externally powered or on-board powered systems using electricity or another fuel source to maintain a temperature-controlled environment inside an insulated enclosure under thermostatic regulation (e.g. cold rooms, refrigerators, temperature-controlled trucks, refrigerated ocean and air containers).

Advanced phase change materials (PCMs): Temperature stabilizing media (sometimes referred to as refrigerants), chemically engineered so that their latent heat of fusion occurs at a temperature other than 0 °C, phasing from one state of matter to another (i.e. liquid to solid) at a pre-formulated temperature. Such materials typically comprise oils, salts, or paraffin.

Ancillary packaging components: Packaging elements used to protect the TTSPP and support or enhance performance of the completed package. This may include retainers, dunnage, secondary protective packaging, and temperature data logging devices.

Chemical indicators: (also called markers or phase-change indicators), are generally impregnated onto a paperboard substrate. These indicators, sometimes referred to as critical temperature indicators, are based on a phase change or chemical reaction that occurs as a function of temperature. Examples include liquid crystals, waxes, polymers, and lacquers that change phase, and thereby their appearance, as a function of temperature. Chemical temperature threshold indicators are irreversible and are suitable for high or low temperatures. Temperature threshold indicators show a response and typically are single-use devices. These indicators provide a signal only when exposed to temperatures higher than (ascending indicator) or lower than (descending indicator) a predetermined threshold temperature.

Coolant: Ice, water, water-based gel, phase-change material, dry ice, or other substance, typically encapsulated in a rigid or flexible plastic container, used to maintain a predefined temperature range inside a passive container during transport operations.

Critical control point (CCP): A step or procedure at which controls or checks can be applied to prevent or reduce a hazard or risk to an acceptable

or critical level. In the context of distribution and handling of time- and temperature-sensitive pharmaceutical products, CCPs are typically defined for those activities where time and temperature abuse may occur or where critical processes that can affect the performance of the packaging solution or containment system are at risk.

Electronic data integrator (EDI): A hybrid electronic instrument intelligently programmed like an electronic temperature indicator (ETI) with the report/data producing capabilities of an electronic data logging monitor (EDLM) that combines the features and functions of a go/no-go device (like an indicator) with the record retention and data tracking facility of an EDLM but with greater granularity and data management flexibility. It uses preprogrammed temperature threshold intelligence to integrate post-analytic functional steps that are typically performed by trained personnel.

Electronic data logging monitor (EDLM): A small portable device that measures and stores temperature readings at predetermined time intervals by means of an electronic sensor. They have programmable alarm capabilities, integrated displays, and can create reports and graphs which may be permanently stored, shared and analysed via proprietary hardware, software, desktop application or through hosted databases.

Electronic temperature indicator (ETI): A compact, portable device that measures, temperature over time by means of a built-in sensor. They come in a wide range of forms, features, configurations, cost and levels of performance. Their composition consists of four basic components: a thermistor sensor, a microprocessor, a memory chip, and a power source (lithium battery).

Electronic temperature monitoring and event logger system: System for recording and reporting air and/or product temperatures, with optional facilities for recording and reporting specific events such as door opening or defrost cycles, and for issuing alarms. Such systems may be user-programmable and may also be remotely monitored via a satellite link.

External distribution: Transport of TTSPPs through various steps in the customer's supply chain (i.e. transport from a pharmaceutical manufacturer's distribution centre, to commercial customers (including wholesalers, retailers and buying groups), to clinical facilities or direct to the patient). Contrast with *internal distribution*.

Internal distribution: Transport of a TTSPP within a pharmaceutical manufacturer's internal supply chain (i.e. all internal transport from the manufacturing plant to the packaging plant and onwards to warehouses and distribution centres). Contrast with *external distribution*.

Passive systems: Systems which maintain a temperature-controlled environment inside an insulated enclosure, with or without thermostatic regulation, using a finite amount of preconditioned coolant in the form of chilled or frozen gel packs, phase change materials, dry ice or others.

Pharmaceutical product: Any product intended for human use or veterinary product intended for administration to food producing animals, presented in its finished dosage form, that is subject to control by pharmaceutical legislation in either the exporting or the importing state and includes products for which a prescription is required, products which may be sold to patients without a prescription, biologicals and vaccines. Medical devices are not included.[1]

Refrigerated vehicle: Road transport vehicle such as a van, truck or semi-trailer whose isolated thermostatically controlled cargo compartment is maintained at a temperature different (lower or higher) than that of the external ambient conditions. The environment inside the cargo compartment may be *temperature-controlled* or *temperature-modified*.

Refrigeration equipment: The term "refrigeration" or "refrigeration equipment" means any equipment whose purpose is to lower air and product temperatures and/or to control relative humidity.

Service level agreement (SLA): A service level agreement or contract is a negotiated agreement between the customer and service provider that defines the common understanding about materials or service quality specifications, responsibilities, guarantees and communication mechanisms. It can either be legally binding, or an information agreement. The SLA may also specify the target and minimum level performance, operation or other service attributes.[2]

Shipping system: All components constituting a completed package including: the outer shipping container, all internal ancillary packaging components and temperature-stabilizing medium.

Standard operating procedure (SOP): A set of instructions having the force of a directive, covering those features of operations that lend themselves to a definite or standardized procedure without loss of effectiveness. Standard operating policies and procedures can be effective catalysts to drive performance improvement and improve organizational results.

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[1] Definition from WHO/QAS/08.252 Rev 1 Sept 2009. Proposal for revision of WHO good distribution practices for pharmaceutical products – Draft for comments.

[2] Definition from IATA. *2013/2014 Perishable Cargo Regulations (ePCR) & Temperature Control Regulations (eTCR)*

Storage temperature: The temperature range listed on the TTSPP label, and within the regulatory filings, for long-term storage.

Temperature excursion: An event in which a TTSPP is exposed to temperatures outside the range(s) prescribed for storage and/or transport. Temperature ranges for storage and transport may be the same or different; they are determined by the product manufacturer, based on stability data.

Temperature stabilizing medium: Ice or gel packs; gel bricks, bottles or pouches; cool water or warm water packs, phase change materials, dry ice, rapid evaporation media which limit exposure of packed product to excessively high or low temperatures during transport: also referred to as refrigerants or coolants.

Temperature-controlled: Includes any environment in which the temperature is actively or passively controlled at a level different from that of the surrounding environment, within precise predefined limits.

Temperature-modified: Includes any environment in which the temperature is predictably maintained at a level different from that of the surrounding environment, but is not actively or passively controlled within precise predefined limits.

Time and temperature -sensitive pharmaceutical product (TTSPP): Any pharmaceutical good or product which, when not stored or transported within predefined environmental conditions and/or within predefined time limits, is degraded to the extent that it no longer performs as originally intended.

Time-temperature integrators (TTIs): Are generally chemically impregnated onto a pulp or paperboard substrate. Their reaction rate or diffusion process is used to estimate a temperature equivalent integrated over time. Thus, TTIs provide a measure of accumulated heat rather than instantaneous temperature such as a spike or critical threshold (see *chemical indicators*). The reactions are irreversible – once a colour change, colour development, or diffusion process has taken place, exposure to low temperatures will not restore the indicator to its original state. They change colour, or are marked by a hue progression in intensity (generally from light to dark) in response to cumulative changes in temperature, such as heat, at a rate dependent on the Arrhenius equation. A TTI accumulates all of the temperature conditions experienced by the product to which it is affixed. The colour development can be customized based on the known stability of the product, and in much the same way that most biologicals and pharmaceuticals degrade when exposed to heat - faster at higher temperatures, and slower at lower temperatures.

Unit load device (ULD): A container used for consolidating and transporting cargo aboard aircraft. They are generally made of aluminium and/or fibreglass

and configured to fit the geometry of an aircraft and are considered part of the aircraft frame. Large active systems fall into the category of ULD. There are two basic sizes classified by the airline industry: LD-3 and LD-9.

Validation: Documented testing performed under highly controlled conditions, demonstrating that processes, methods, and systems consistently produce results meeting pre-determined acceptance criteria.[3]

Work instruction: Describes *how* to complete a specific task. Contrast with an SOP which describes *who* (title or department) should carry out a series of tasks, and in what sequence.

[3] Parenteral Drug Association (PDA). Technical Report No. 39: Guidance for temperature controlled medicinal products: Maintaining the quality of temperature-sensitive medicinal products through the transportation environment. Bethesda (MD): PDA; 2007.

1. Introduction

This technical supplement has been written to amplify the recommendations given in sections 6.4 and 6.5 of WHO Technical Report Series No. 961, 2011, Annex 9: *Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products*.[4] It provides guidance on how to condition, load and handle equipment used to transport time- and temperature-sensitive pharmaceutical products (TTSPPs) in order to maintain these products within a predefined operating temperature range. The supplement covers refrigerated and temperature-controlled transport vehicles and active and passive shipping containers for road and air transport. Fixed storage systems, such as cold rooms and refrigerators, are outside the scope of this document.

The following Technical Supplements are also relevant:

- *Qualification of shipping containers*
- *Qualification of temperature-controlled road vehicles*
- *Temperature and humidity monitoring systems for transport operations*
- *Transport route profiling qualification*.

1.1 Requirements

Packaging systems should be qualified before use. Generally speaking, the shipper is responsible for ensuring product temperature compliance during transport.

1.2 Objectives

The objective of the Technical Supplement is to:

- Provide a general technical introduction to the active and passive packaging and transport systems used for distributing TTSPPs.
- Describe how to pack temperature-controlled products correctly in active and passive systems and how to manage their transit through the transport environment.
- Describe the correct use of the various types of temperature and humidity monitoring device.
- Describe the documentary evidence that should be supplied to regulatory authorities and other interested parties so that quality assurance and regulatory compliance can be demonstrated and maintained.

[4] http://apps.who.int/medicinedocs/documents/s18683en/s18683en.pdf

1.3 Target readership

This technical supplement is intended for all those responsible for the transport of TTSPPs through the supply chain from one fixed storage point to another.

Staff responsible for transport operations need to understand the importance of temperature stability for pharmaceutical products, have a sound working knowledge of applicable logistics and transport methodologies within their organizations, and they should understand the basic concepts of packaging thermodynamics and good documentation practice. They should have a good knowledge of the various types of temperature monitoring device used in the transport environment, together with their strengths, weaknesses and appropriate uses. They must also be able to train and supervise junior staff so that they are able to carry out the tasks described below in a reliable and consistent manner.

2. Guidance

This section describes the processes that need to be followed to ensure safe transport of TTSPPs by road and air. These two transport modes involve similar processes. The options available for ocean transport are not covered here because this transport mode has its own unique requirements. For general guidance on importation and port clearance procedures readers should also refer to Chapter 24 of Managing Drug Supply (MDS)-3: *Managing access to medicines and other health technologies – importation and port clearing* and to the International Air Transport Association (IATA) document: *Temperature control regulations: The global standard for the safe transportation of healthcare products by air*.

2.1 Associated materials and equipment

The physical components of a quality-assured, temperature-controlled transport system are the active and passive packaging systems, described below, in which products are placed during transport. Temperature monitoring devices are also a key component. The specific characteristics and uses of these devices are described in the companion Technical Supplement: *Temperature and humidity monitoring systems for transport operations*.

2.2 Available shipping systems

Temperature control during ground air or ocean transport can be maintained using either active or passive shipping systems, as described below.

2.2.1 Refrigerated vehicles – temperature-controlled

This category includes vans, rigid trucks and semi-trailers that have an insulated, thermostatically-controlled cargo compartment and a dedicated refrigeration unit capable of maintaining the labelled temperature range of the products being transported. Vans and small rigid trucks typically have refrigeration units powered directly by the vehicle's engine. Larger rigid vehicles and semi-trailers have independent diesel-powered refrigeration units. Both types may also have electrical back-up so that they can be mains-powered while parked. All refrigerated vehicles should be equipped with an on-board electronic temperature monitoring and event logger system.

Refrigerated vehicles must be properly qualified for their designated operating environment. They should only be used in operating environments that are able to manage the equipment, and over roads which will not damage the vehicles. Refer to Technical Supplement: *Qualification of temperature-controlled road vehicles*.

2.2.2 Refrigerated vehicles – temperature-modified

These are similar to temperature-controlled refrigerated vehicles, except that the vehicle itself simply moderates the ambient temperature, either by heating or cooling. The transported product is generally packed in a qualified passive shipping system designed to keep it within the labelled temperature range. The temperature-modified environment in the vehicle serves to extend the autonomy of the passive shipping system and protect the product from temperature extremes. Care must be taken not to subject the packages to refrigerated temperatures (e.g. +2.0 °C to +8.0 °C) for extended periods because this leads to a risk of freezing the package contents. Ideally, operators should avoid exposure of active and passive packaging to temperatures below +15.0 °C. In order to ensure this, temperature-modified vehicles should preferably be equipped with an on-board electronic temperature monitoring and event logger system.

The recommendations on use described above for temperature-controlled refrigerated vehicles also apply.

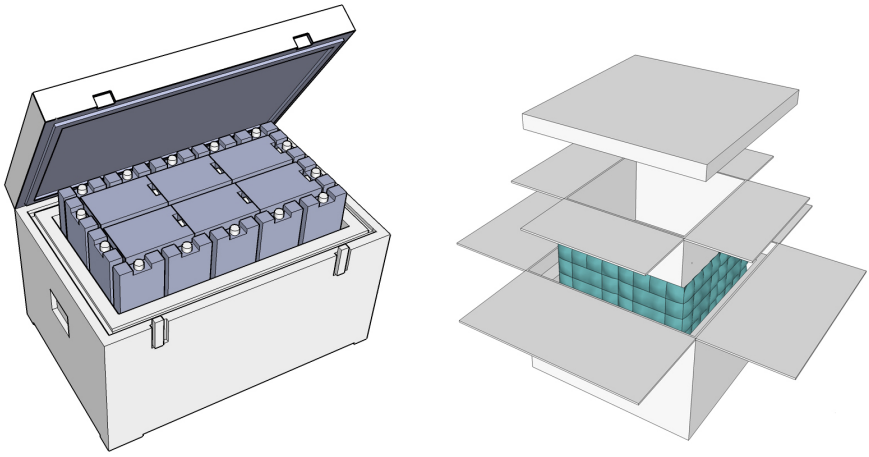
2.2.3 Passive shipping systems

A particular advantage of passive systems in resource-constrained settings is that safe transport of TTSPPs can reliably be provided over poor roads. They can also be used for air transport. A properly qualified passive shipping system can be used to maintain effective temperature control of the pharmaceutical product at ambient transport temperatures. However these systems should only be used after the route and container has been qualified – see Technical Supplements: *Transport route profile qualification and Qualification of shipping containers*.

Passive shipping systems consist of a combination of insulated material and temperature-stabilizing media. When correctly configured, such a combination can keep the internal contents of the package within a specified temperature range for a predefined period of transport, without reliance on mechanical assistance. The packages are sealed in specific configurations and do not rely on any further human or mechanical intervention to perform to a specific level during transport. However, they have a predefined transport life and consequently delivery must always be achieved within this period.[5] Figure 1 shows an example of both a reusable and a single-use passive container.

[5] O'Donnell K, Wright A. Good distribution practices by air, road & ocean: Workbook and resource guide. Farnham: Exelsius; 2013.

Figure 1
Generic passive containers with coolant packs



Reusable container

Disposable insulated carton

The impact-resistant outer layer of disposable packaging is typically made of corrugated fibreboard which protects the insulated lining. Reusable containers have a durable outer shell, insulating core and inner liner designed to last for multiple journeys. In both cases, thermal control is provided by coolants which are chosen to maintain a specific temperature range inside the package; depending on the type of container these may either be disposable or reusable. The packaging system is completed by other ancillary packaging components used as separators, dividers or dunnage.

The temperature of the product within the package is maintained by applying the physics of conduction and convection in conjunction with the stored latent heat of fusion from the refrigerant. All passive packaging systems contain a finite amount of refrigerant energy. More sophisticated packaging uses advanced phase change materials (PCMs) instead of water-based gel packs or simple water-packs.

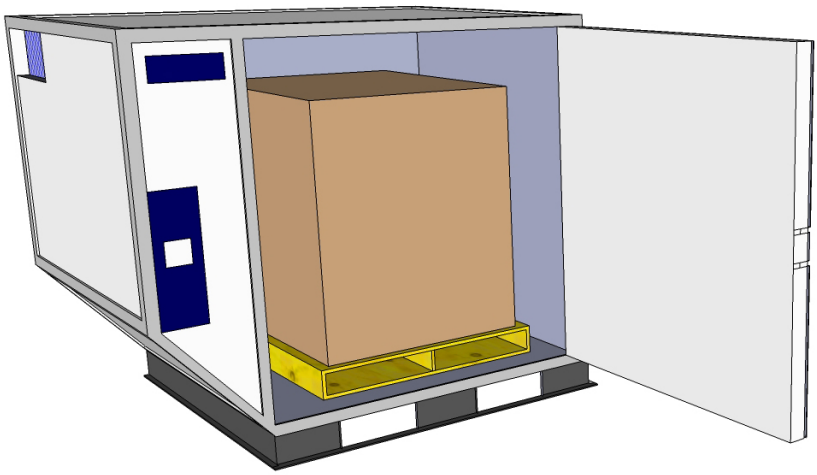
2.2.4 Active shipping systems for air transport

The typical active shipping system is a dedicated portable container. Such containers come in two types: systems with cooling only, and systems with both heating and cooling.[6] The temperature-stabilizing medium in active shipping systems comprise dry ice (cooling types only) or use phase change

[6] Heat-only units are also available, but unlikely to be relevant for TTSPP transport.

materials (heating and cooling types) as a means to provide temperature control; alternatively compressor-driven cooling systems are also widely used. These containers are either powered by on-board batteries, or use an external electrical source to run on-board compressors or heat pumps. Thermostatic control is used to activate the cooling or heating mechanism and circulating fans help to maintain temperature within specified limits around the enclosed product. Larger containers are generally leased from the manufacturer, or by an air or ocean carrier, or by a third-party logistics service provider. Figure 2 shows an example.

Figure 2
Active air transport container – type LD3



2.3 Quality agreements

A safe and reliable temperature-controlled transport operation starts with a comprehensive user requirements specification (URS), informed by a thorough risk assessment exercise. This can be used as a basis for contracting out services via a service level agreement (SLA), or for managing an in-house operation. However the service is provided, suitable standard operating procedures (SOPs), standard checklists and associated work instructions must be developed and used to control each shipment.

2.3.1 User requirements specification

The shipper is responsible for ensuring that the packaging and the mode(s) of transport used to distribute TTSPPs are capable of maintaining the products within their specified temperature and humidity ranges. Accordingly, the detailed

requirements for each type of transport operation must be fully defined and suitable transport service providers identified and appointed. The correct way to do this is to draw up a URS. This document should clearly define the following:

- the temperature and humidity parameters that must be maintained for each product or product type; these parameters are determined by the product label, or when acceptable, the manufacturer's stability data;
- the transport mode and/or vehicles to be used;
- the required level of service;
- acceptable levels of risk to product and performance;
- the types of packaging;
- the types of temperature and humidity monitoring devices to be used and the acceptable level of accuracy of these devices;
- specific service actions such as go/no-go decision-making in the event of a temperature excursion event, or more complex analytical data gathering and reporting requirements.

The URS can be used as a basis for developing SOPs and work instructions for in-house transport operations, and/or an SLA for contracted-out transport services.

2.3.2 Service level agreements (SLAs)

Shippers and other transport service provider stakeholders should operate under the mutually agreed terms of an SLA, which specifies the target and minimum levels of performance, service, operation or other attributes as set out in the URS. In-house transport services should be controlled with a similar level of rigour. An SLA should contain the following elements:

Introduction:

- purpose and objective of the SLA;
- parties to the agreement;
- commencement date;
- duration of the agreement;
- definitions and glossary of terms.

Scope of work:

- standard service(s);
- non-standard service(s);

- place of service, including collection and delivery locations;
- changes to service.

Compensation:

- fee tariff;
- invoicing arrangements;
- payment terms.

Performance monitoring and reporting:

- managing changes in key personnel;
- service benchmarks;
- service monitoring and reporting mechanisms;
- service review meetings.

Problem management:

- support services;
- problem identification;
- problem escalation procedures.

Duties and responsibilities:

- customer/client personnel, facilities, resources;
- training for specialized equipment/tasks;
- approvals.

Warrantees and remedial action:

- allocation of responsibilities between the parties to the agreement;
- liability;
- resolution procedures and penalties for noncompliance.

2.4 Identifying and controlling risk

A key characteristic of transport operations is the number of "touch-points", "hand-offs" or process and service exchanges between the various organizations and individuals involved. The TTSPP is at the greatest risk of improper handling during these exchanges. For this reason they are defined as critical control points (CCPs) in the transport supply chain. Table 1 lists the actions that may need to be taken to reduce risk or hazard to an acceptable level at each of the key stages in an air freight operation – not all of these will be mandatory for every shipment and every shipping system.

Table 1
Cold store maintenance schedule

Critical handling process	Type of risk control
Product preparation and conditioning at shipper's location	• Electronic temperature monitoring of storage facility, i.e. refrigerator, freezer, cold room, warehouse. Humidity monitoring where appropriate • Defined conditioning and staging time specifications for packaging components – temperature and duration, compliant with DQ and OQ
Product loading at shipper's location	• Defined process, checksheet • Application of IATA TTSPP label • Defined actions in the event of delays
Ground transport from shipper location	• Use of refrigerated or temperature-controlled vehicle – Temperature defined and preconditioned before loading – Electronic temperature monitoring; humidity monitoring where appropriate • Serviceability checks on equipment • Defined actions in the event of delays
Warehousing (en route)	• Use of IATA Standard Acceptance Checklist for Time and Temperature Sensitive Healthcare Shipment • Temperature monitoring; humidity monitoring where appropriate • Availability of batteries, electrical connections or dry ice to maintain correct temperature of active containers • Availability of sub-zero, refrigerated or controlled room temperature storage when required • Defined storage instructions • Defined actions in the event of delays, and mishaps en route
Airport tarmac/apron	• Minimize time exposed to ambient temperatures • High priority ramp handling • Covered storage when transiting through multiple airports • Use of passive protection tools such as thermal blankets • Defined actions in the event of delays

Table 1 *continued*

Critical handling process	Type of risk control
Aircraft hold	• Avoid positioning near cargo door • Cargo hold temperatures maintained between +15.0 °C and +25.0 °C • NOTOC (notification to captain) defining cargo hold temperature setting or use of dry ice in active containers

DQ, design qualification; OQ, operational qualification; IATA, International Air Transport Association.

Wherever temperatures are read and recorded, the record should be to a minimum of one decimal place.

The following subsections set out the content of the checklists needed to operate three distinct types of shipping system:

- refrigerated and temperature-controlled vehicles;
- passive shipping systems sent by road and air transport;
- operations using both passive and active containers.

Each of the checklists follows the same sequence: pre-shipment actions; actions on the day of shipment at the point of origin; actions during transit; actions on the day of arrival at the destination and, finally, post-shipment actions.

2.5 Managing refrigerated road shipments

Refrigerated and temperature-controlled transport services are often supplied by a third-party service provider specializing in such transport. Alternatively, the service may be directly operated by a national public health system, a parastatal company, or by a public–private partnership (PPP). In all cases it is important that service providers conduct regular, periodic training of responsible personnel, whether directly employed or subcontracted.

It is essential that the correct infrastructure is in place to support the operation of these specialized vehicles. Specifically, all regular drop-off points should have a compatible electrical connection to power the cooling unit, especially for smaller vehicles where the refrigeration circuit is powered by the vehicle engine generator. This is critical in settings that involve overnight stops. In instances where the refrigeration unit is powered solely by the vehicle's engine, the engine must remain running at all times to avoid interruptions in maintaining proper temperature.

Vehicles should be equipped with an integrated continuous temperature monitoring and data logging system. Ideally, retrievable temperature data logging devices should also be packed with the shipped product.[7]

The action sequence below is based on risk mitigation principles. Some steps may be omitted or modified, provided there is a technical justification for doing so.

Pre-shipment actions:

a. Arrange booking, pick-up time and location.
b. Obtain confirmation from the consignee to ship the product (e.g. purchase order or requisition).
c. Verify product dimensions and determine the type of container required.
d. Book the shipment with the prequalified and approved freight forwarder or transport service provider.
e. Specify temperature requirements.
f. Prepare shipping documentation and checklists.
g. Ensure that the designated vehicle is in good working order, that its service record is up-to-date and that the driver has carried out the relevant daily safety inspection.

Shipping day: actions at point of origin:

a. Confirm booking, pick-up time and location.
b. Pack the product in its correct tertiary package and attach temperature-monitoring devices to suit the routing requirements. Keep product under proper storage conditions until the time of dispatch.
c. Ensure that the vehicle is fully operational and that the cargo area is clean and odour-free.
d. Before loading, precondition the product and the refrigerated vehicle's cargo area to the required transport temperature. Keep loading door(s) closed until it is time to load the product.
e. Ensure that the thermostatic controller on the transport vehicle is set to the required temperature and ensure that the temperature recording device(s) are operating properly.

[7] For details of suitable systems refer to Technical Supplement: Temperature and humidity monitoring systems for transport operations.

f. Check that the vehicle's refrigeration unit is operating properly and that the temperature has stabilized. Drivers must ensure that the correct temperature setting has been selected.
g. Load product without delay. Do not overload the vehicle. Allow for air circulation around all sides of the product. Properly block and brace the load, as shown in **Annex 1**, to avoid shifting during transit. Close door(s) and apply security seal and/or lock if required.
h. Whenever possible, ensure that the driver is able to supervise the loading process.
i. If the refrigeration unit has been operating on mains electric power during loading, make sure that the engine-powered refrigeration system is operating correctly and that the temperature has stabilized within predefined limits before releasing.
j. Provide clear instructions to the driver concerning the correct load temperature, handling and transport requirements.
k. Provide emergency contact information to the driver.
l. Ensure that all paperwork and checklists are completed by responsible parties.

Actions during transit:

a. Cooling units must remain active throughout the entire journey, including during stops and rest periods.[8]
b. Energy-saving modes/options of the cooling unit should not be used.
c. Vehicle payload doors must only be opened during loading and unloading and opening time must be kept to a minimum.[9]
d. To avoid theft and tampering, only use secure parking areas.
e. Minimize the time during which the vehicle is unattended by the driver.

Arrival day: actions at destination point(s):

a. Ensure priority unloading.
b. Remove product from the vehicle and move it immediately to a location providing the correct temperature-controlled storage conditions.

[8] At some border crossing points there may be restrictions on the running of engines owing to defined maximum permissible noise levels (dB).

[9] Note that doors may have to be opened for customs inspection.

c. Retrieve temperature data from the driver. Refer to the companion Technical Supplement: *Temperature and humidity monitoring systems for transport operations*.
d. Record temperature upon arrival. Communicate any deviations to the appropriate personnel.
e. When the product is received, the consignee should retrieve and deactivate the temperature monitors accompanying the shipment and read and download the data. *Note:* If temperature monitors are not packed with the product, the data from the on-board temperature recording system should be downloaded, or a print-out obtained from the driver and attached to the arrival forms.
f. Ensure all checklists and arrival forms are completed by the responsible parties.

Post-shipment actions:

Forward completed checklists and completed arrival forms, including electronic temperature data files to the appropriate personnel.

2.6 Managing passive container road shipments

Wherever possible, covered vehicles should be used for transporting passive containers so that shipments are not exposed to the sun or to the elements. The action sequence below is based on risk mitigation principles. Some steps may be omitted or modified, provided there is a technical justification for doing so.

Pre-shipment actions:

a. Ensure that there are sufficient quantities of all packaging components to accommodate the shipment on the shipping day.
b. Ensure that all components have been conditioned to the correct temperature (i.e. temperature-stabilizing media, whether frozen or refrigerated).
c. Ensure that the designated vehicle is in good working order, that its service record is up-to-date and that the driver has carried out the relevant daily safety inspection.

Shipping day – actions at point of origin:

a. Prepare and pack product in its designated secondary or ancillary packaging.
b. Assemble the passive shipping system and pack and load the product in accordance with approved site procedures.

c. Add temperature data loggers or temperature indicators if required. Place in close proximity to the product. Do not allow them to come into contact with temperature-stabilizing media.
d. Ensure that all paperwork and checklists are completed by the responsible parties.

Actions during transit:

a. Vehicles should be parked in a secured parking area during rest stops; wherever possible, vehicles should be parked in the shade.
b. Containers must not be opened during transit.

Arrival day: actions at destination:

a. Open packaging, remove product from its passive shipping system and move it immediately to the correct temperature-controlled storage conditions.
b. Retrieve and deactivate temperature monitors for data retrieval.
c. Ensure all checklists and arrival forms are completed by responsible parties.

Post-shipment actions:

a. Forward completed checklists to appropriate personnel, including electronic temperature data files.
b. Dispose of, recondition or reuse packaging as appropriate.

2.7 Introduction to air transport

Where infrastructure is insufficient or geographical obstacles are present, and also because it is faster, air transport is frequently the mode of choice for long distance transport of TTSPPs, both between and within countries. The IATA's *Perishable cargo regulations and temperature control regulations* comprise the industry's framework for complying with good distribution practices (GDP).[10] The purpose of the regulations is to:

- describe the packaging and systems used in pharmaceutical product distribution;
- identify potential risks to product quality;
- recommend critical control points to reduce these risks;

[10] GDP requirements embrace the activities of pharmaceutical manufacturers, shippers, 3PLs, 4PLs, cargo agents, freight forwarders, independent air carriers, airlines, packagers and active solution platform providers, warehousing agents and ground handlers.

- describe operating agreements such as SLAs or quality agreements;
- define and delineate quality management system requirements;
- define labelling requirements;
- recommend handling procedures.

Many air carriers offer "branded services" with defined procedures based on GDP to meet the specific needs of TTSPPs. Any variation or deviation from such a branded service should be defined and negotiated beforehand in a specific SOP.

In order to minimize risk, shippers should always collaborate with the air carrier, either directly or through the designated freight forwarding agent. This is essential in order to define and agree the service level needed to meet the shipper's requirements.

Temperature control within the cargo holds of most aircraft is limited and wide variations can occur throughout the hold; these variations depend upon placement, location, time at altitude, and the duration of the flight. However, the greatest and most frequent exposure to temperature variation occurs on the airport tarmac when goods are exposed to the elements before aircraft loading, or during unloading. Every precaution should be taken to limit this exposure. Shippers are encouraged to work with their air service suppliers to minimize the time TTSPPs wait on the tarmac.

2.7.1 Types of air carrier

Four different business models are used for the transport of TTSPPs by air: legacy carriers, integrators, cargo-only carriers, and charters. Within each category, carriers will have different service offerings and service levels tailored to the handling requirements of specific cargo.

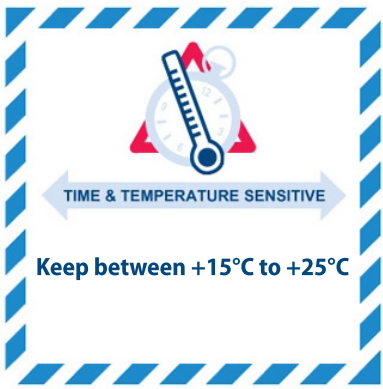
- *Legacy carriers (commercial airlines):* These companies operate both passenger and cargo services and have the advantage that they service a wide range of destinations. Most of these carriers subcontract services for aircraft handling, ground handling and warehousing operations. A commercial airline's cargo business usually comes from freight forwarders and the airline involvement is limited to airport-to-airport activities. Some may offer road feeder services at the origin or destination. Otherwise, a freight forwarding agent coordinates that effort.
- *Integrators:* These operate large-scale door-to-door mail and express delivery services. Their product offerings are integrated under a single brand identity (e.g. FedEx, DHL and UPS). They generally deal directly with the shipper rather than a freight forwarder.

- *Cargo only carriers:* These companies do not carry passengers; they operate dedicated freighter aircraft and can carry large cargo payloads. Their networks are not as extensive as those of the commercial airlines, which operate on a hub and spoke model. Cargo only carriers often sign contracts with large, international freight forwarders to ensure cargo space availability. Their services may include ground pick-up and delivery, so fewer stakeholders are involved. As with commercial airlines, their ground handling operations are often subcontracted.
- *Charters:* These operators allow shippers to choose between a full or partial charter. Freight forwarders with a need for dedicated space on certain high-volume trade lanes often employ charters.

2.7.2 Air transport labelling for TTSPPs

Since July 2012, the IATA time and temperature sensitive label, shown in Figure 3, has been mandatory for the transport of health-care cargo shipments. There are however, specific conditions for proper use of the label. These can be found in the current edition of the IATA *Perishable cargo regulations,* Chapter 17: Logistics for temperature sensitive healthcare products.

Figure 3
Example of IATA time and temperature sensitive label



Actual size 10 cm × 10 cm

The principal rules for the correct use of the label are as follows:

- Shipments must be booked under the proper handling code and as temperature-controlled health-care cargo in accordance with the IATA Perishable Cargo Regulations

- The label must be used for health-care products only.
- The label may be applied to both active and passive shipping systems.
- The lower half of the label must indicate the external handling temperature range or limit (minimum and maximum) that the package can be exposed to during transport.
- The label is attached to a consignment which has been specifically booked as a time- and temperature-sensitive health-care product.[11]
- The temperature range on the label must match the temperature range or limit stated on the air waybill (AWB), SLA and/or SOP.
- The text must be in English and temperatures must be shown in degrees Celsius.
- The label must be applied by the shipper or by his or her designated agent.
- Only one label is required. This must be visible on the outermost means of containment (box, over-pack, or unit load device (ULD)).

2.8 Air transport processes

Air transport operations must be tightly managed. In addition to the tasks that must be carried out to ensure the safe arrival of a specific shipment (see Section 2.9) a number of higher level precursor and recurrent actions need to be taken. These are described below.

The shipper should:

- conduct regular periodic training of personnel;
- maintain an SLA with the appropriate stakeholders and transport service providers;
- qualify the transport process to the extent possible in collaboration with the forwarder and carrier.

The freight forwarder should:

- conduct regular periodic training for directly employed and subcontracted personnel;
- maintain a quality and security management system that meets the shipper's requirements;
- maintain SLAs with subcontractors.

[11] This is a premium service beyond that offered for general cargo.

The air carrier and ground handlers should:

- Conduct regular periodic training of directly employed and subcontracted personnel to ensure correct handling and storage of TTSPPs during transit.

The consignee should:

- conduct regular periodic training of personnel.

2.9 Managing air shipments

The actions described below apply to both active and passive shipping systems, unless specifically identified. As previously noted, some steps may be omitted or modified, but only if there is a technical justification for doing so.

Pre-shipment actions:

a. Obtain confirmation from the consignee to ship the product (e.g. purchase order or requisition).
b. Verify product dimensions and determine the type of container required.
c. Notify the freight forwarder of the shipping date and book the shipment. The freight forwarder must coordinate the transport chain and booking with the air carrier in accordance with the IATA perishable cargo regulations (PCR).
d. Communicate instructions to the freight forwarder regarding pick-up, transport and handling requirements, including transport temperature requirements.
e. Prepare shipping documentation, including checklists and AWB and review with the freight forwarder.
f. Arrange ground transport to airport at point or origin.

Shipping day – actions at point of origin:

a. Condition and pack the product and place activated temperature monitors within the load.
b. Label the product box to indicate the temperature range within which the shipment must be handled (see IATA PCR Chapter 17.10 for details).
c. Transport product to the freight forwarder or departure airport in a temperature-controlled truck or refrigerated vehicle. The freight forwarder must obtain the shipper's approval before implementing any changes that could affect GDP or the quality of the shipped product.

Shipping day – actions at departure airport by freight forwarder:
The following action sequence assumes that the freight forwarder loads the ULD.

a. *Active dry-ice systems only:* Load the amount of dry ice recommended by the device manufacturer into the dry ice bunker. Install fresh D-cell batteries.
b. *Active systems:* Set the thermostatic controller to the desired temperature. Ensure that the container is operating properly and wait until the temperature stabilizes.[12]
c. Load product into container. Ensure correct build-up of the ULD and labelling in accordance with written instructions. Do not overload. Allow for air circulation all around product, including at the bottom. Strap the load to the floor or wall stanchions to avoid shifting during transit.
d. Close door(s). Apply security seal or lock.
e. Activate and position any exterior (ambient) temperature monitors.
f. Secure paperwork in the external clear-view envelope.
g. Before releasing the container to the airline, ensure that it is operating correctly and that the temperature has stabilized.
h. Transport to the airline warehouse and hand off. From this point onward the airline is responsible for maintaining the appropriate ambient temperature during storage and flight, for checking power and for re-icing the container if required, in accordance with the relevant SOP.
i. Ensure priority handling onto the aircraft.
j. Ensure all checklists are completed by responsible parties in accordance with the SOP.
k. Forward the AWB and other paperwork and instructions to the appropriate personnel.
l. Maintain tracking and traceability of the product throughout the transport process.
m. Promptly resolve and communicate any deviations.
n. Perform customs brokerage. If the ULD is opened for customs inspection the inspection must be as short as possible and the doors must be secured again afterwards. If seals were changed, inform the shipper and/or the consignee accordingly.

[12] Active ULDs are sometimes loaded at the shipper's site. A security check may then be conducted at the departure airport. This involves opening the ULD and scanning the contents.

Shipping day: actions at by air carrier and ground handlers:

a. Review the AWB and other shipping documentation with the freight forwarder and ensure that it complies with the regulations and procedures relevant to the carrier and country.
b. Comply with the programmed flight schedule and ensure that adequate space is available in the cargo hold.
c. Communicate any delays or problems to the freight forwarder.
d. Update any temperature monitor log sheets.
e. Store the product in conditions that are within the defined temperature range on the label and AWB.
f. Minimize the time that elapses between warehouse and aircraft loading or unloading (tarmac time).
g. Handle active and passive shipping systems in accordance with shipper's instructions.
h. Load the consignment into the aircraft. Wherever possible, avoid placing temperature-sensitive freight near the aircraft cargo door.
i. Maintain recommended cargo hold temperature settings.
j. Transport the product from the departure airport to the destination airport.
k. Store the product at transit airports in an area kept within the specified handling temperature range.
l. Inform the freight forwarder of arrival.

Arrival day: actions at destination:

a. Ensure priority unloading of TTSPPs from the aircraft.
b. Handle active and passive shipping systems in accordance with shipper's instructions.
c. Store the product at the arrival airport in an area kept within the specified handling temperature range.
d. *Active systems:* Check that the container is operating properly. Re-ice and replace batteries if required.
e. *Active systems:* Record the temperature as shown on the outside display panel.
f. The freight forwarder assists with customs clearance and logs receipt of the product from the service provider.
g. Provide clear instructions for either unloading the container at the airport or for transporting it to the consignee.
h. Inspect goods for physical damage and evidence of temperature abuse.

i. Ensure all checklists are completed by responsible parties.
j. Consignee receives product, retrieves and deactivates electronic data logging monitors (EDLMs) for data retrieval, if applicable.

Post shipment actions:

a. Forward completed checklists to appropriate personnel, including the electronic temperature data files.
b. Transport the empty container to the ground handler, check for damage and functionality.
c. Return any packaging and/or temperature monitoring devices, if applicable.
d. The forwarder collects all pertinent data, checklists, and other necessary documents, to complete shipment.

A similar international shipping procedure has been developed by the United Nations Children's Fund (UNICEF) Supply Division specifically for shipping vaccines in passive containers. This process, together with the UNICEF vaccine arrival report form, is described in EVM-SOP-E1-02: *Vaccine arrival procedures*.

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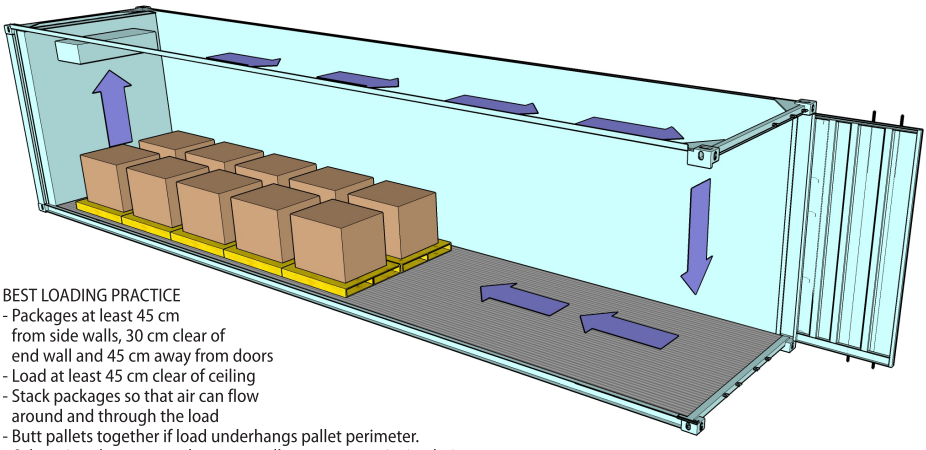
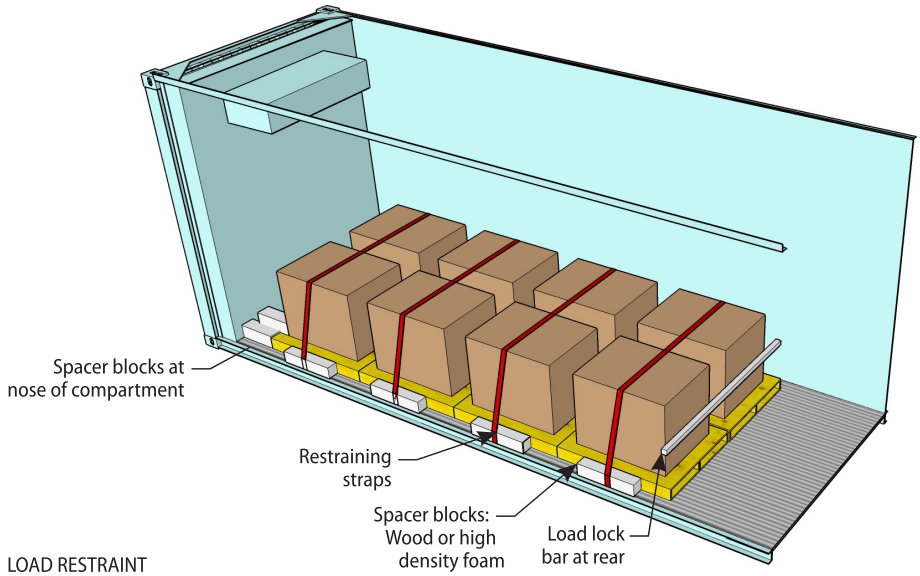
Annex 1

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



LOAD RESTRAINT

Revision history

Date	Change summary	Reason for change	Approved

Supplement 13

Qualification of shipping containers

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

Annex 9: Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products

May 2015

Contents

Abbreviations

ASTM	American Society for Testing and Materials
DQ	design qualification
EDLM	electronic data logging monitor
ISPE	International Society for Pharmaceutical Engineering
ISTA	International Safe Transit Association
OQ	operational qualification
PDA	Parenteral Drug Association
PQ	performance qualification
SOP	standard operating procedure
TTSPP	time- and temperature-sensitive pharmaceutical product
URS	user requirement specification

Acknowledgements

The authors of this document are Kevin O'Donnell, Exelsius Cold Chain Management Consultancy and member of the United States Pharmacopeia Expert Committee on Packaging, Storage and Distribution, 2010–2015 cycle, Ben VanderPlas, Sonoco ThermoSafe and Bill Mayer, Minnesota Thermal Science.

Glossary

Active systems: Externally powered or on-board powered systems using electricity or another fuel source to maintain a temperature-controlled environment inside an insulated enclosure under thermostatic regulation (e.g. cold rooms, refrigerators, temperature-controlled trucks, refrigerated ocean and air containers).

Advanced phase change materials (PCMs): Temperature stabilizing media (sometimes referred to as refrigerants), chemically engineered so that their latent heat of fusion occurs at a temperature other than zero ° Celsius, phasing from one state of matter to another (i.e. liquid to solid) at a pre-formulated temperature. Such materials typically comprise oils, salts, or paraffin.

Ancillary packaging components: Packaging elements used to protect the TTSPP and support or enhance performance of the completed package. This may include retainers, dunnage, secondary protective packaging, and temperature data logging devices.

Associated components: Articles of packaging that are typically intended to deliver the dosage form to the patient but are not stored in contact with the dosage form for its entire shelf life. These components are packaged separately in the market package and are either attached to the container upon opening or used only when a dose is to be administered. Examples are measuring spoons, dosing cups, and measuring syringes.

Cryogenic dry/vapour shipper: A temperature-controlled insulated packaging container or system compatible with liquefied gases such as nitrogen used for maintaining extremely low temperatures during shipping. A porous medium internal to the shipping container absorbs and contains all the free flowing liquid and does not allow it to come into contact with the product – a process known as "charging". A fully charged and undamaged dry/vapour shipper containing nitrogen can maintain −196 °C for up to 10 days, depending on the unit size.

Design qualification (DQ): The process of obtaining and documenting evidence that the premises, equipment and supporting systems and processes have been designed in accordance with the requirements for good manufacturing practices (GMP).[1]

Dunnage: Loose packing material used to protect TTSPPs from damage during transport.

[1] WHO Technical Report Series, No. 961, 2011. Annex 3: WHO good manufacturing practices for pharmaceutical products: main principles.

Electronic data logging monitor (EDLM): A small portable device that measures and stores temperature at predetermined time intervals by means of an electronic sensor. They have programmable alarm capabilities, integrated displays, and can create reports and graphs which may be permanently stored, shared and analysed via proprietary hardware, software, desktop application or through hosted databases.

Electronic temperature monitoring and event logger system (EDLM): System for recording and reporting air and/or product temperatures, with optional facilities for recording and reporting specific events such as door-opening or defrost cycles, and for issuing alarms. Such systems may be user-programmable and may also be remotely monitored via a satellite link.

External distribution: Transport of TTSPPs through various steps in the customer's supply chain (i.e. transport from a pharmaceutical manufacturer's distribution centre, to commercial customers (including wholesalers, retailers and buying groups), to clinical facilities or direct to the patient). Contrast with *internal distribution*.

Installation qualification (IQ): The process of obtaining and documenting evidence that the premises, equipment and supporting systems have been provided and installed in compliance with their design specifications.

Internal distribution: Transport of a TTSPP within a pharmaceutical manufacturer's internal supply chain (i.e. all internal transport from the manufacturing plant to the packaging plant and onwards to warehouses and distribution centres). Contrast with *external distribution*.

Maximum payload: The amount of product intended to be shipped with the most amount of thermal mass.

Minimum payload: The amount of product intended to be shipped with the least amount of thermal mass.

Operational qualification (OQ): The process of obtaining and documenting evidence, under controlled conditions, that the premises, equipment and supporting systems operate in accordance with their design specifications.

Packout: An assembled package that includes the product to be shipped (alternatively, simulated product in its primary packaging form used for its commercial presentation, the insulated shipper or container, any and all necessary auxiliary and/or associated components and ancillary packaging components such as temperature stabilizing medium, secondary packaging, partitions, bubble wrap, data loggers or other temperature monitoring units, and dunnage.

Passive systems: Systems which maintain a temperature-controlled environment inside an insulated enclosure, with or without thermostatic regulation, using a finite amount of preconditioned coolant in the form of chilled or frozen gel packs, phase change materials, dry ice or others.

Performance qualification (PQ): The process of obtaining and documenting evidence that the premises, equipment and supporting systems, as connected together, will consistently perform in accordance with the approved process method and specifications.

Pharmaceutical product: Any product intended for human use or veterinary product intended for administration to food producing animals, presented in its finished dosage form, that is subject to control by pharmaceutical legislation in either the exporting or the importing state and includes products for which a prescription is required, products which may be sold to patients without a prescription, biologicals and vaccines. Medical devices are not included.[2]

Prequalified shipping container system: A packaging container or packaging system in which a DQ and OQ have already been established and documented by the manufacturer and the user has acquired sufficient documentation to meet their user requirement specification (URS).

Qualification protocol: A written and approved plan detailing how a qualification will be conducted including test parameters, product characteristics, equipment and acceptance criteria.

Qualification: Action of proving that any premises, equipment and supporting systems work correctly and actually lead to the expected results. The meaning of the word *validation* is sometimes extended to incorporate the concept of qualification.

Refrigeration equipment: The term "refrigeration" or "refrigeration equipment" means any equipment whose purpose is to lower air and product temperatures and/or to control relative humidity.

Seasonal packaging solution: (Also called a dedicated packaging solution). A packed shipping container system, whose effective performance in different seasons requires more than one packing configuration. These configurations depend on seasonal variants such as summer and winter or hot and cold season exposure.

[2] Definition from WHO/QAS/08.252 Rev 1 Sept 2009. Proposal for revision of WHO good distribution practices for pharmaceutical products – Draft for comments.

Secondary pack or carton or market package: The package presentation intended for the end-user (e.g. bottle + cap liner + dose cap + leaflets + carton) but not including packaging used solely for transport purposes (e.g. *Tertiary carton* or *Insulated shipper*). The secondary pack may contain multiple units of product.

Shipping system: All components constituting a completed package including: the outer shipping container, all internal ancillary packaging components and temperature stabilizing medium.

Standard operating procedure (SOP): A set of instructions having the force of a directive, covering those features of operations that lend themselves to a definite or standardized procedure without loss of effectiveness. Standard operating policies and procedures can be effective catalysts to drive performance improvement and improve organizational results.

Storage temperature: The temperature range listed on the TTSPP label, and within the regulatory filings, for long-term storage.

Temperature excursion: An event in which a TTSPP is exposed to temperatures outside the range(s) prescribed for storage and/or transport. Temperature ranges for storage and transport may be the same or different; they are determined by the product manufacturer, based on stability data.

Temperature stabilizing medium: Ice or gel packs; gel bricks, bottles or pouches; cool water or warm water packs; phase change materials, dry ice, and rapid evaporation media which limit exposure of packed product to excessively high or low temperatures during transport: also referred to as refrigerants or coolants.

Temperature-controlled: Includes any environment in which the temperature is actively or passively controlled at a level different from that of the surrounding environment within precise predefined limits.

Time and temperature-sensitive pharmaceutical product (TTSPP): Any pharmaceutical good or product which, when not stored or transported within predefined environmental conditions and/or within predefined time limits, is degraded to the extent that it no longer performs as originally intended.

Transport temperature profile: Anticipated ambient temperature variation and duration to which a TTSPP may be exposed during transport.

Universal packaging solution: A shipping container whose proper performance does not require more than one packing configuration regardless of seasonal variants such as summer and winter or hot and cold exposure.

User requirement specification (URS): The attributes assigned by the user in advance of a qualification test to establish minimum performance limits. Sometimes referred to as a *functional requirements document*.

Validation: Documented testing performed under highly controlled conditions, demonstrating that processes, methods, and systems consistently produce results meeting predetermined acceptance criteria.[3]

[3] Parenteral Drug Association (PDA) Technical Report No. 39: Guidance for temperature controlled medicinal products: Maintaining the quality of temperature-sensitive medicinal products through the transportation environment. Bethesda (MD): PDA; 2007.

1. Introduction

This technical supplement has been written to amplify the recommendations given in sections 6.8.1, 6.8.3 and 6.8.4 of the WHO Technical Report Series No. 961, 2011, Annex 9: *Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products*.[4] The document covers the qualification of all single-use and reusable active, passive, hybrid, and cryogenic dry/vapour shipping containers or systems used for the transport of a time- and temperature-sensitive pharmaceutical product (TTSPP) in external distribution.

The principal focus is on performance qualification (PQ). The document also includes a brief introduction to the requirements and technical resources needed for design qualification (DQ) and operational qualification (OQ) because these activities need to be understood by those responsible for assessing and procuring third-party container systems. The supplement should be read in conjunction with the companion Technical Supplement, *Transport route profiling qualification*.

What is qualification?

In the context of this series of Technical Supplements, *qualification* is an inspection and testing process used to establish that a piece of equipment or a physical installation is fit for purpose in the operational context within which it will be used. There are typically three stages in the process. Each stage must be successfully completed before the next one begins.

Design qualification (stage 1 for equipment): Establish by laboratory testing under tightly controlled conditions that a specific item of equipment performs in accordance with the user requirement specification (URS). While design qualification demonstrates compliance with the URS and associated test protocols, it does not prove that the equipment will be suitable in a specific operating environment because the URS and the test procedures are unlikely to reflect the full range of operating conditions.

[4] http://apps.who.int/medicinedocs/documents/s18683en/s18683en.pdf

Installation qualification (stage 1 for installations): Establish by documented inspection and testing that an installation[5] that has been assembled in a specific location is fully in accordance with the URS and installation drawings.

Operational qualification (stage 2): Establish by further documented testing under controlled conditions that this equipment or installation is likely to perform as intended in the operating environment in which it will be used.

Performance qualification (stage 3): Carry out a final stage of documented testing to establish with a high degree of assurance that the equipment or installation, together with all associated systems, does indeed perform as intended under routine operating conditions.

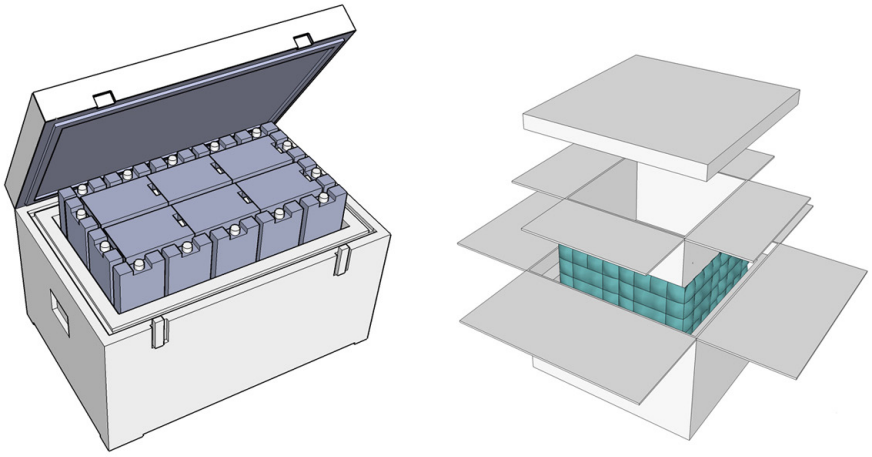
1.1 Requirements

Transport operators and end-users need to be sure that TTSPPs are delivered in container systems that are capable of maintaining a predefined internal temperature range during transport, can minimize product degradation as a result of temperature-sensitivity, and can meet the product stability profile requirements stated by the pharmaceutical manufacturer. Regulatory authorities and other interested parties require documented evidence that such assurance and compliance can be demonstrated and maintained.

Every shipping container system must be fully qualified to show that it is "fit for purpose" and capable of maintaining a TTSPP within the temperature range needed to meet the product manufacturer's stability profile, under the anticipated transport conditions. Qualification must also demonstrate that the system can sustain handling and transport while protecting the physical integrity of the product. These multiple challenges are described in the user requirement specification (URS). Figure 1 illustrates the two types of passive container covered by this document. Active containers come in many types and are not illustrated.

[5] The installation will typically incorporate components that have been design qualified.

Figure 1
Generic passive containers with coolant packs (WHO)



Reusable container

Disposable insulated carton

As noted above, qualification consists of three sequential testing stages: DQ, OQ, and PQ. If the container manufacturer can demonstrate that the product has already passed an appropriate conformity assessment or that it has already been independently prequalified by a standard-setting organization such as the World Health Organization (WHO),[6] the DQ stage is not required. In both these cases DQ will have formed part of a pre-purchase assessment process. If the system manufacturer is additionally able to supply a satisfactory OQ report, which meets the end-user's needs, the OQ stage may also be dispensed with.

1.2 Objectives

The objective of this technical supplement is to provide advice on how to ensure that shipping container systems meet the performance parameters defined in the URS with a high degree of certainty and repeatability.

1.3 Target readership

This document is intended for use by anybody who is responsible for maintaining quality during the process of assessing, procuring and using TTSPP shipping container systems.

[6] See: http://apps.who.int/immunization_standards/vaccine_quality/pqs_catalogue/categorypage.aspx?id_cat=18

These parties need to appreciate the importance of temperature stability for pharmaceutical products, have a sound working knowledge of applicable logistics and transportation methods within their organizations, and understand the basic concepts of packaging thermodynamics.

Those who are responsible for conducting qualification testing must be capable of operating the equipment necessary to complete the tests and be familiar with, and follow, good laboratory documentation practices.

2. Guidance

It is most likely that the users of this document will be assessing the performance of an existing "prequalified" packaging system. Section 2.1 gives a brief introduction to all three types of qualification – DQ, OQ and PQ. The remainder of the guidance section focuses principally on PQ. However, if a DQ and OQ have not been completed, it is the responsibility of the user to complete these two stages before proceeding to the PQ. In all cases, a URS must be written and approved before testing takes place. Any deviations from the test protocols must be documented as an "exceptional condition".

2.1 The three stages of qualification

Before any qualification stage is begun, carry out a risk assessment to identify the environmental conditions and the distribution lanes through which the proposed container will travel. This process helps ensure that the proposed qualification procedure will match the intended use. Consider the anticipated scenarios when deciding on the qualification temperature ranges.

Full details of the packaging assembly must be defined, tested and documented for each of the three stages of the qualification process. These details include the thermal conditioning regime for system components and the products being transported, product loading arrangements and the location of temperature monitor(s). Test dates should also be recorded in all qualification reports.

It is strongly recommended that both minimum and maximum product loads are tested at each stage. The test loads should be chosen to represent the products which will be transported. In most cases the lowest thermal mass products are the ones most susceptible to temperature change. Accordingly, the minimum load in a test should represent a shipment of a minimum quantity of the lowest thermal mass product and the maximum load should represent a full payload of this same product.

Qualification must also take account of the transport route(s) and modes of transport and the anticipated ambient temperature profile over the duration of transport. Transport time is measured from the time the completed package is closed and sealed at the point of departure, until the package is opened at the point of arrival in the recipient's temperature-controlled store.

2.1.1 Design qualification

All new shipping container systems must successfully meet the predefined acceptance criteria set out in an approved DQ protocol or project scope document. In the case of a system that is already prequalified, it will only be necessary to repeat the DQ stage if the system specifications do not appear fully to meet the

requirements of the end-user's original URS. This URS should clearly define product load specifications, ambient temperature profiles, shipping duration, and allowable product temperature range. Other performance characteristics may also need to be included in the document.

DQ takes place under laboratory-controlled conditions against an approved DQ protocol. This protocol defines the tests needed to evaluate basic design requirements, constraints and suitability for use. Any deviations from the protocol must be documented as an "exception condition". At a minimum, the following list of packaging configurations should be tested unless otherwise specified:

a. one heat profile, maximum product load;
b. one heat profile, minimum product load;
c. one cold profile, maximum product load;[7]
d. one cold profile, minimum product load.

The purpose of these tests is to collect enough evidence to establish that the container design concept is sound and to justify moving on to the OQ stage. OQ should not take place until the DQ stage is satisfactorily completed including simulated transport stress tests (vibration and drop), which are a required part of DQ.

2.1.2 Operational qualification

As with the DQ stage, an OQ may not be required when a prequalified shipping system is used. In such cases, an OQ report can often be provided by the container system supplier, either free of charge, or for a fee. However, if a prequalified shipping system OQ report is relied upon, no substitutions or modifications to the design or packaging can be made and the performance of the system as set out in the report must demonstrably meet or exceed all the specifications in the end-user's URS.

If substitutions or modifications to the design or packaging are made an OQ must be carried out; there may also be other reasons to justify the need for an OQ. OQ is carried out under laboratory-controlled conditions and the OQ protocol must clearly define the packout arrangements and the acceptance criteria for the shipping system(s) to be qualified. As a minimum, the protocol must define the following test criteria as derived from the initial risk assessment exercise: transport duration, acceptable temperature range, payload details, ambient temperature profiles, location of temperature monitoring devices,

[7] Products that can safely be shipped frozen do not need cold profile testing.

location of refrigerant, and refrigerant conditioning specifications. Other test criteria may also need to be included – for example transport and stress tests (vibration and drop) – and the OQ protocol must be approved by all stakeholders before qualification testing takes place. To demonstrate repeatable performance the OQ tests must be carried out in triplicate and must successfully meet the acceptance criteria in every one of these tests.

When the OQ is complete, prepare a final report; this should document the test performance and compare the results with the acceptance criteria set out in the OQ protocol.

2.1.3 Performance qualification

The final stage of qualification – the focus of this document – is the PQ; this stage is mandatory in all cases, except where every shipment on every route is monitored. PQ is conducted as a field test in the real operating environment. A PQ protocol must be developed to document the process and define the acceptance criteria; these criteria should be similar to those defined in the DQ and OQ protocols. The PQ protocol should be representative of existing shipping operations and must include:

- the number of "ship-to" locations;
- the number of "ship-from" locations;
- the number of shipments to be tested;
- the time of year the shipments are to occur.

As with the OQ, PQ tests must be performed three times, and must successfully meet the acceptance criteria in every instance, in order to demonstrate repeatable performance. Once the PQ is complete, prepare a final report which documents the test results and compares them with the PQ acceptance criteria.

2.1.4 Re-qualification of reusable container systems

Reusable shipping container systems, with and without interchangeable parts, should periodically be re-qualified to ensure that the thermal performance has not been adversely affected as a result of age, change in chemical properties, physical damage, off-gasing, evaporation of temperature stabilizers, or other potential performance loss. Generally, this re-qualification process is user-defined; typically it is done on annually, on the basis of a risk assessment, or when there is some significant change in transport operations.

2.2 Associated materials and equipment

Below is a list of the minimum equipment required to perform a DQ, OQ or PQ qualification.

2.2.1 Test equipment for design and operational qualifications

This DQ and OQ list is primarily for information purposes. It can be used to check that the correct equipment has been used for testing prequalified containers that are put forward for PQ.

- Thermal test chamber(s) of sufficient size to accommodate the package(s) being tested. The chamber(s) must be capable of simulating ambient temperatures within the required ambient temperature profile ranges and able to condition components; both within a tolerance of ±3 °C.
- A multi-channel temperature data logger with a sufficient quantity of thermocouples capable of producing a permanent record of temperature and elapsed time with an acceptable operating tolerance of ±0.5 °C for temperatures > −18 °C and ±0.8 °C for temperatures ≤ −18 °C;

  or a portable electronic temperature data logging monitor (EDLM) capable of producing a permanent record of temperature and elapsed time with an acceptable operating tolerance of ±0.5 °C, over a temperature range approximately between −20 °C and +50 °C.[8]
- Calibration bath – for thermocouple verification.
- Weighing scale with an accuracy of ±5% of the gross container weight.
- Packaging materials.

Other equipment may also be needed for testing package robustness, resistance to vibration and the like.

2.2.2 Test equipment for performance qualification

- Portable electronic temperature data logging monitors (EDLMs) capable of producing a permanent record of temperature and time elapsed with an acceptable operating tolerance of ±0.5 °C, over a temperature range approximately between −20 °C and +50 °C.
- Complete packout configurations.

Wherever possible, use the same equipment for the PQ tests as is used for the OQ tests.

[8] The accuracy of EDLMs that use thermistors as a means of determining temperature is less at the outer limits of their operating range. It is acceptable to have wider tolerances for temperatures outside this range: e.g. ±0.8 °C for temperatures ≤ −18 °C, or ±2 °C for temperatures below −40 °C (dry ice shipments).

2.3 The performance qualification test protocol

A PQ protocol details the field testing procedures needed to verify the results of an OQ in the intended distribution environment. A comprehensive protocol should include the following sections:

2.3.1 Protocol title

Describe the project in the main title of the form. In the subtitle identify the test container, test product, temperature range, duration and any other unique information. Make it clear that this is a PQ protocol.

2.3.2 Protocol approvals

List the project stakeholders. Include company, position, space for signatures, and dates.

2.3.3 Introduction

Briefly describe the packaging configuration and the acceptance requirements of the test system. Define all abbreviations used in the protocol and provide a glossary of technical terms if needed.

2.3.4 Purpose

The purpose statements should begin with the words: "the purpose of this xxx protocol is…" followed by a brief description of why the protocol was written and what information the document contains. Include details of the test container, product loads, coolants, temperature range, and duration.

2.3.5 Scope

Describe the qualification strategy, how the testing will be performed and how the data will be represented. This should include full details of the test container, minimum and maximum product load specifications, and the number of tests to be performed against which ambient profiles.

2.3.6 Acceptance criteria

Define the required product temperature range and minimum required transport duration. Any applicable product temperature excursions and other design priorities or constraints must also be defined.

2.3.7 Responsibilities

List the personnel or groups responsible for protocol writing, execution, testing, sampling, report writing, and approval. If a contract testing facility is to be used, identify the facility in this section.

2.3.8 Test procedure

Describe the necessary step-by-step procedures used to perform the PQ:

a. unique test number identification;
b. equipment and materials – list all items used;
c. list all test material preparation or conditioning requirements;
d. identify test equipment – include applicable calibration certificates;
e. describe the packout details;
f. describe temperature monitoring or thermocouple probe placement;
g. include isometric drawings, graphics or photographs as needed to describe packouts, location of EDLMs and the like;
h. define the frequency of data recording;
i. include shipping and receiving documents, when applicable;
j. provide a signature log for all personnel who perform, verify, or review the protocol;
k. record packout start-time, weight, and end-time on a worksheet;
l. record monitor location, test date, ship-to and ship-from locations and end-time.

2.3.9 Data analysis

Define how the data generated from the testing will be interpreted. This includes:

- Equilibration duration – the time required by the shipping container system to reach the required temperature before shipment.
- Temperature of the product during testing gathered from the EDLMs.
- Total time during which product remains within the required temperature range (in hours and minutes)

Record all temperature data in degrees Celsius.

2.4 The performance qualification test

A PQ uses actual field shipments to verify that the DQ and OQ processes are representative and can effectively and consistently provide reproducible results. Carrying out a proper PQ can take from several weeks up to several months. This period depends on the quality of the test protocol design, the test parameters, and the number of tests performed.

At least three tests per shipping container are required for both the minimum and maximum product payload. At a minimum, each series of tests should be conducted during the warmest and coolest part of the year.

Additional tests can be conducted at other times during the year, or whenever new containers are being considered for adoption. If the test container is to be used on multiple routes, determine and choose the worst-case shipping lane and transport method; this will expose the container system to maximum stress in terms of temperature and duration.

Table 1 gives an example of a test schedule with one container type, two packaging configurations and two temperature profiles; this combination requires a minimum of 12 tests to be performed. The number of tests needed increases significantly with each added variable. It is therefore wise to minimize the number of container sizes and the variability in packing configurations.

Table 1
Example of a test schedule

Ambient profile	Load configuration	Test number
Hot profile	Minimum product load	Test 1-1
		Test 1-2
		Test 1-3
	Maximum product load	Test 2-1
		Test 2-2
		Test 2-3
Cold profile	Minimum product load	Test 1-1
		Test 1-2
		Test 1-3
	Maximum product load	Test 2-1
		Test 2-2
		Test 2-3

The principal steps in the PQ testing process are as follows:

a. For each season (summer and winter or hot season and cold season), identify representative "ship-from" locations.[9] For each of these departure points identify the "ship-to" location that provides the most challenging shipping route. Use these locations for the PQ study.

[9] See Technical Supplement: Transport route profiling qualification.

Typically, the chosen routes will include those combining the longest duration with the most extreme temperatures, both hot and cold.

b. Once the worst-case shipping lanes are defined, list these in the PQ protocol for future reference, together with the justification for their selection.

c. Wherever possible, use actual product as the payload for PQ testing. Another option is to use expired samples of the real product because this eliminates the risk of damage to potent, in-date TTSPPs. If real or expired product is not available, use a suitable and representative payload substitute. The substitute payload should have a similar thermal mass, freezing point and packaging as the actual payload.[10]

d. Before conducting each test, condition the payload at its standard storage temperature for the minimum time needed to achieve a uniform temperature throughout the payload (e.g. +2 °C to +8 °C for 24 hours). The conditioning equipment being used should be able to maintain the temperature set point within ±3 °C and the conditioning process should be monitored and documented to ensure compliance.

e. At the same time condition the temperature stabilizing medium in accordance with an approved SOP or according to the container manufacturer's instructions. The conditioning equipment being used should be able to maintain the temperature set point within ±3 °C.

f. Use portable EDLMs to acquire the temperature data during the test. The logger(s) should be calibrated (National Institute of Standards and Technology (NIST) traceable) and have a valid calibration certificate; this certificate should be included in the final report. The resolution of the logger(s) should be 0.1 °C or better. The accuracy should be ±0.5 °C, over a temperature range approximately between −20 °C and +50 °C.[11]

g. Programme the EDLMs so that the maximum temperature-recording interval is no greater than 30 minutes (5 or 10 minutes is better). The logger's sensor response time should be less than the chosen recording interval and the device should have sufficient memory to hold all recorded data for the entire shipment at the chosen recording interval.

[10] This could be a low-value "placebo" product chosen to reduce the risk of financial loss.

[11] See footnote 10 above.

h. Precondition the EDLMs at the standard storage temperature (see d. above). An alternative approach is to activate the EDLM's "delayed start" function so that the device does not begin recording until it has cooled down to the temperature of the payload.

i. Use a minimum of one interior payload EDLM and one external ambient EDLM for each test. The payload EDLM(s) should be positioned to capture temperature variation or temperature stratification within the payload space. Multiple loggers may be needed to achieve this.

j. Place the interior EDLMs in direct contact with the payload whenever possible. If a single logger is used it should be located in the spot most susceptible to failure; in many cases this is likely to be a top corner of the payload. If OQ test data are available, consult the OQ report to determine the most susceptible locations. The exterior logger should be positioned so that the logger's sensor has reasonable, unobstructed access to the ambient air while taking into account the need to protect the device from damage during shipment. This can be used to correlate air to product temperature data by referring back to the OQ testing from the PQ results.

k. Pack each shipping container in accordance with the manufacturer's instructions, or in the same manner that the product was packed in the OQ (if applicable).

l. After proper conditioning, place the temperature stabilizing medium and the test payload into the payload space. Secure the interior EDLM(s) in the predetermined location(s). Tape the devices in position so that they cannot shift during transit. If required, insert non-insulating dunnage before closing the container to prevent the payload from shifting in transit. Attach and secure the external ambient logger in the predetermined location. The readings from this device enable the analyst to identify how the ambient temperature profile relates to any temperature excursions that may occur in the payload.

m. Seal the container with packaging tape (or tamper-evident tape) and ship along the predetermined route.

n. In addition to monitoring thermal performance, the PQ should include a visual inspection of the physical condition of the container at the destination. The container should show no sign of damage or deterioration at the point of arrival. Physical damage may adversely affect thermal performance, product handling, storage or safety.

o. A PQ worksheet should be completed for each individual container system. This should document the preconditioned refrigerant and product loads, the time at which the container system was fully packed and sealed, the serial number of the EDLM(s), the package weight (net and gross), and the shipment tracking number.

p. Provide clear instructions to the individual(s) responsible for receiving the container. These instructions should fully describe any post-test analyses and give instructions on downloading and distributing the temperature data obtained from the EDLM(s).

q. When the PQ shipping studies are complete, analyse the temperature data and other information collected and determine whether the acceptance criteria, defined by the PQ protocol, have been met.

r. Compile a final report which details the findings of the study. Refer to section 2.5 for information on what to include in this report.

It is recommended that a PQ study should be repeated on a risk-based frequency cycle. In addition, carry out periodic monitoring to determine the need for additional PQ. This helps give assurance that there have been no changes to the distribution lanes used for the transport of the temperature-sensitive products. Any such changes may impact the temperature performance of the load.

Re-qualification should be considered whenever there are changes to components, shipping routes or shipping duration.

2.5 The performance qualification report

The PQ report should summarize the test data and performance characteristics established during qualification testing and provide conclusions based upon these data. The report should include a copy of the test protocol with signature log, complete equipment list, and material specifications. In addition, it should include test graphs, complete test worksheets, all testing data, equipment calibration certificates, and any applicable deviation reports.

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Revision history

Date	Change summary	Reason for change	Approved

Supplement 14

Transport route profiling qualification

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

Annex 9: Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products

May 2015

Contents

Abbreviations

CCP	critical control point
EDLM	electronic data logging monitor
ISTA	International Safe Transit Association
PDA	Parenteral Drug Association
TTSPP	time- and temperature-sensitive pharmaceutical product

Acknowledgements

The authors of this document are Kevin O'Donnell, Exelsius Cold Chain Management Consultancy and member of the United States Pharmacopeia Expert Committee on Packaging, Storage & Distribution 2010–2015 cycle, Susan Li, United Parcel Service, Mark Maurice, Sensitech, and Ken Maltas, Sally Eggers, Sonoco ThermoSafe and Andrew Garnett, WHO consultant.

Glossary

Ambient temperature: The uncontrolled prevailing temperature(s) within a specific environment or series of environments, such as a supply chain.

Conditioned ice-pack: An *ice-pack* that has been allowed to warm at ambient temperature until some liquid water is present inside the pack. The pack is correctly conditioned as soon as the ice core is able to move inside the pack when it is shaken. The effective temperature of a *conditioned ice-pack* in this state is 0.0 °C.[1]

Cool life (test): The empty passive container is stabilized at +43.0 °C and loaded with cool water-packs which have been stabilized at +5.0 °C for a minimum of 24 hours. Cool life is measured from the moment when the container is closed, until the temperature of the warmest point inside the storage compartment first reaches +20.0 °C, at a constant ambient temperature of +43.0 °C.[1]

Cool water-pack: A water-pack cooled to a temperature of +5.0 °C before use.[1]

Critical control point (CCP): A step or procedure at which controls or checks can be applied to prevent or reduce a hazard or risk to an acceptable or critical level. In the context of distribution and handling of time- and temperature-sensitive health-care products, CCPs are typically defined for those activities where time and temperature abuse may occur or where critical processes that can affect the performance of the packaging solution or containment system are at risk.

Design qualification (DQ): The process of obtaining and documenting evidence that the premises, equipment and supporting systems and processes have been designed in accordance with the requirements for good manufacturing practices (GMP).[2]

Electronic data logging monitor (EDLM): A small portable device that measures and stores temperature at predetermined time intervals by means of an electronic sensor. They have programmable alarm capabilities, integrated displays, and can create reports and graphs which may be permanently stored, shared and analysed via proprietary hardware, software, desktop application or through hosted databases.

External distribution: Transport of TTSPPs through various steps in the customer's supply chain (i.e. transport from a pharmaceutical manufacturer's distribution centre, to commercial customers (including wholesalers, retailers

[1] Source: WHO Performance, Quality and Safety (PQS).

[2] WHO Technical Report Series, No. 961, 2011. Annex 3: WHO good manufacturing practices for pharmaceutical products: main principles.

and buying groups), to clinical facilities or direct to the patient). Contrast with *internal distribution*.

Ice-pack: A water-pack that has been frozen to a temperature between −5.0 °C and −25.0 °C before use.[1]

Internal distribution: Transport of a TTSPP within a pharmaceutical manufacturer's internal supply chain (i.e. all internal transport from the manufacturing plant to the packaging plant and onwards to warehouses and distribution centres). Contrast with external distribution.

Lanes: Transport routes from a point of origin to a destination.

Operational qualification (OQ): The process of obtaining and documenting evidence, under controlled conditions, that the premises, equipment and supporting systems operate in accordance with their design specifications.

Passive systems: Systems which maintain a temperature-controlled environment inside an insulated enclosure, with or without thermostatic regulation, using a finite amount of preconditioned coolant in the form of chilled or frozen gel packs, phase change materials, dry ice or others.

Pharmaceutical product: Any product intended for human use or veterinary product intended for administration to food producing animals, presented in its finished dosage form, that is subject to control by pharmaceutical legislation in either the exporting or the importing state and includes products for which a prescription is required, products which may be sold to patients without a prescription, biologicals and vaccines. Medical devices are not included.[3]

Qualification protocol: A written and approved plan detailing how a qualification will be conducted including test parameters, product characteristics, equipment and acceptance criteria.

Qualification: Action of proving that any premises, equipment and supporting systems work correctly and actually lead to the expected results. The meaning of the word *validation* is sometimes extended to incorporate the concept of qualification.

Shipping system: All components constituting a completed package including: the outer shipping container, all internal ancillary packaging components and temperature stabilizing medium.

Standard operating procedure (SOP): A set of instructions having the force of a directive, covering those features of operations that lend themselves to

[3] Definition from WHO/QAS/08.252 Rev 1 Sept 2009. Proposal for revision of WHO good distribution practices for pharmaceutical products – Draft for comments.

a definite or standardized procedure without loss of effectiveness. Standard operating policies and procedures can be effective catalysts to drive performance improvement and improve organizational results.

Study protocol: A document detailing the scope, objectives and operational specifics of a series of tests or data collection (study) written and approved in advance of execution of the study.

Temperature excursion: An excursion event in which a TTSPP is exposed to temperatures outside the range(s) prescribed for storage and/or transport. Temperature ranges for storage and transport may be the same or different; they are determined by the product manufacturer, based on stability data.

Temperature-controlled: Includes any environment in which the temperature is actively or passively controlled at a level different from that of the surrounding environment within precise predefined limits.

Time and temperature-sensitive pharmaceutical product (TTSPP): Any pharmaceutical good or product which, when not stored or transported within predefined environmental conditions and/or within predefined time limits, is degraded to the extent that it no longer performs as originally intended.

Transport temperature profile: Anticipated ambient temperature variation and duration to which a TTSPP may be exposed during transport.

Validation: Documented testing performed under highly controlled conditions, demonstrating that processes, methods, and systems consistently produce results meeting predetermined acceptance criteria.[4]

Vented shipping box: A container used to house an EDLM in order to record ambient air temperatures during transport, designed and constructed to maximize the airflow between the outside and inside of the container during the transport period. The container may be an integral part of a product shipment. Alternatively, if shipped separately, its overall size and weight should be similar to the container(s) used for the product(s) which are being monitored – this will ensure that the same handling practices are used.

Warm life (test): The empty passive container is stabilized at +18.0 °C and loaded with *warm water-packs*, which have been stabilized at the same temperature for a minimum of 24 hours. Warm life is measured from the moment when the container is closed, until the temperature of the coldest point inside the storage compartment first reaches 0.0 °C at a constant ambient temperature of –20.0 °C.[5]

[4] PDA Technical Report No. 39: Guidance for temperature controlled medicinal products: Maintaining the quality of temperature-sensitive medicinal products through the transportation environment, 2007.

[5] Source: WHO PQS

Warm water-pack: A water-pack typically stabilized at room temperature, up to a recommended maximum of +24.0 °C. Warm-packs are used for the transport of freeze sensitive vaccines when the ambient temperature is below 0.0 °C.

1. Introduction

This technical supplement has been written to amplify the recommendations given in section 6.8.3 and 6.8.4 of WHO Technical Report Series No. 961, 2011, Annex 9: *Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products*.[6]

Understanding the environment through which a TTSPP must travel is essential for successful logistics operations, for package design, and for maintaining the quality of the pharmaceutical product during external distribution. The best way to understand the temperature hazards that may occur during external distribution is to collect actual temperature data from representative parts of the supply chain. This process dispels assumptions, and can reveal weaknesses, risks and trends within the transport system. This document describes a method for profiling transport routes which is simple to understand and to execute; it is based on an approach called the "heat under the curve" method. Other techniques can also be used, but these tend to be more complex.

Temperature information gathered from a route profiling exercise can be used to develop representative ambient temperature profiles for specific lanes, modes and durations of transport. Route profiling is a prerequisite for carrying out a statistically representative operational qualification (OQ) or performance qualification (PQ) exercise involving shipping containers and refrigerated vehicles.

This supplement should be read in conjunction with the companion Technical Supplements: *Qualification of shipping containers and Qualification of temperature-controlled road vehicles*.

What is qualification?

In the context of this series of Technical Supplements, *qualification* is an inspection and testing process used to establish that a piece of equipment or a physical installation is fit for purpose in the operational context within which it will be used. There are typically three stages in the process. Each stage must be fully completed before the next one begins.

[6] http://apps.who.int/medicinedocs/documents/s18683en/s18683en.pdf

Stage 1 (for equipment): Establish by laboratory testing under tightly controlled conditions that a specific item of equipment performs in accordance with the user requirements specification (URS). This is *design qualification*. While design qualification demonstrates compliance with the URS and associated test protocols; it does not prove that the equipment will be suitable in a specific operating environment because the URS and the test procedures are unlikely to reflect the full range of operating conditions.

Stage 1 (for installations): Establish by documented inspection and testing that an installation[7] that has been assembled in a specific location is fully in accordance with the URS and installation drawings. This is *installation qualification*.

Stage 2: Establish by further documented testing under controlled conditions that this equipment or installation is likely to perform as intended in the operating environment in which it will be used. This is *operational qualification*.

Stage 3: Carry out a final stage of documented testing to establish with a high degree of assurance that the equipment or installation, together with all associated systems, does indeed perform as intended under routine operating conditions. This is *performance qualification*.

1.1 Requirements

Regulators increasingly require pharmaceutical transport operators to document their shipping practices in a manner which shows that they fully understand their transport process and are able to maintain control over it. As part of the process of validating these practices, the PQ of shipping containers and refrigerated vehicles should be based on transport route profile(s) which reflect the real distribution environment in a statistically robust manner. Consequently, the initial route profiling exercise should be carried out before actual products are distributed.

1.2 Objectives

The objective of the Technical Supplement is to provide a step-by-step methodology for establishing the ambient conditions that a package (parcel or palletized products) will experience while it passes through the distribution network. It describes:

[7] The installation will typically incorporate components that have a design qualification.

a. a comprehensive and systematic approach to monitoring temperatures in a distribution system;
b. a protocol for temperature data collection;
c. a method for converting these data into a representative transport route profile with multiple confidence levels;
d. a simple method for estimating the performance of prequalified containers, laboratory tested at constant ambient temperature(s), against an ambient temperature profile;
e. a method for determining representative distribution temperatures for the qualification of shipping systems.

1.3 Target readership

This document should be used by supply chain personnel who are responsible for evaluating the external distribution environment. It should also be read by those responsible for developing or qualifying shipping solutions that are able to address the environmental hazards that will be encountered within a distribution system.

2. Guidance

The fundamental purpose of a transport route profiling study is to collect temperature data that accurately represent real distribution practice. For example: if 90% of all shipments are made between five destinations, the sampling plan must accurately reflect this fact. However, the quantity of data collected should not be so great that it makes data handling and data organization difficult, confusing or subject to error. Once a representative ambient profile has been derived it can be used to qualify a shipping system whose performance aligns with the specific operational context. This supplement sets out the data collection and data analysis process and describes a simple approach for matching a shipping system with a profile – the *degree-hour* method.

Generally speaking, the ambient temperature along a transport route should be sampled once every 10–30 minutes. Increasing the recording frequency improves the resolution of the final data analysis. However, the chosen recording interval is ultimately determined by the overall shipping time and the maximum number of data points that the electronic data logging monitor (EDLM) is capable of capturing.

The sample size should capture the full range of segment variability that occurs in each transport scenario. This includes:

- the range of different carriers used;
- methods of shipment (express versus standard service);
- shipment days;
- mode of transport (ground, air and/or ocean);
- point of origin;
- point of destination;
- seasons (winter and summer or hot season and cold season);
- hemispheric crossings.

The chosen sampling size should reflect the actual application and the practicality of collecting the data. In general, the more data that can be collected, the better, because this will give a more accurate picture of temperature hazards encountered in any given lane. A sample size of 30 trips on a given route over the course of a year is considered to be statistically valid. However such a large sample is not always practical and the decision to choose a smaller sample size for a specific lane is a matter of judgement.[8]

[8] There are currently no recognized tools or references to help with this.

Routine temperature monitoring is a useful tool for finding out why variability occurs during transport. Consequently, once a transport route has been formally profiled, periodic monitoring should continue. This monitoring helps identify risks, process changes and other trending data that may not have been identified in the formal study and which may subsequently affect the performance of transport operations.[9]

2.1 Associated materials and equipment

The following materials and equipment are needed to collect the temperature data needed to profile a transport route:

- EDLMs capable of downloading recorded temperature data to a PC for subsequent analysis. The same EDLM model from a single chosen manufacturer should be used throughout the data collection process. All devices should be identically preprogrammed with the same specifications for data collection frequency, alarms and recording duration. This will greatly simplify data organization and statistical analysis.
- Vented shipping boxes (optional). These boxes are used to protect the EDLMs. If the purpose of the study is to model the small parcel environment,[10] vented boxes are the most representative way to mimic this form of distribution and the unique handling and exposure which occurs. Vented boxes provide better air circulation for sensing the ambient temperature.
- The necessary hardware, software, desktop application or hosted database to extract the data from the device.
- Excel® or other spreadsheet or analytical software capable of organizing and analysing large amounts of temperature data.

2.2 Study protocol

It is essential to write a comprehensive study protocol and have it approved before the study begins. The protocol should cover the scope, purpose and detail of all study procedures and should include the following:

[9] Note that periodic monitoring is not a substitute for a formal route profiling qualification process.

[10] The cubic size and weight of a package can make a significant difference to how it is handled and this can also significantly affect its exposure to temperature. A small parcel does not necessarily experience the same thermal environment as a pallet-sized container. This should be considered and accounted for when gathering temperature data.

a. *Identify the purpose(s) of the study:* These might include any of the following: creation of an ambient temperature profile; collection of temperature or humidity data; identification of weaknesses, gaps or risks in the distribution system; or qualification of a shipping method.
b. *Select the shipping lanes for the study:* Define the origin and destination points of the shipments based on actual distribution needs. Ideally, the destination points would be actual shipping destinations. Alternatively, select logistically similar locations which are better able to receive and return the EDLMs. For example, an office in the destination town might be a more reliable choice than the actual destination warehouse.
c. *Transport modes(s):* Clearly define the mode(s) of transport or shipping methods which are to be used for the study. For example: same-day road delivery; three-day road delivery; international air freight with road pick-up and drop-off; ocean freight.
d. *Define the EDLM logging interval:* This must be the same across all shipments in the study in order to provide equal weight for temperature banding when the data are analysed. The chosen interval should provide sufficient resolution to capture expected temperature fluctuations, without generating unnecessary data. Typically a 10–30-minute logging interval gives adequate resolution and allows identification of the different stages of handling and manipulation along the shipping lane.
e. Determine study duration: i.e. to cover winter, summer, and other seasonal variability. This is to collect data that represent extreme temperature conditions (cold or hot). Ideally, data should be collected all year round (52-week study), but this may not be possible in many cases.
f. *Determine the sample size:* The International Safe Transit Association (ISTA) recommends that at least 25 samples are obtained for each variable. i.e., season (hot or cold), mode of transport as defined in point c, and origin, as defined in point b. Always prepare extra shipments[11] in case some of the test packages do not reach their intended destination or devices are not returned. This generally happens to about 10% of the test shipments.

[11] A "shipment" in this context is a representative sample of product distributed from a single point of origin to a single destination. In the case of a delivery round more than one shipment on the vehicle may be monitored in order to capture route profiling data for different drop-off points.

g. *Choose the study product:* Determine whether the study will use real shipments or simulated shipments. Real shipments represent actual shipments of real products. Simulated shipments use packages without actual products. This applies to both parcel-sized and palletized products.

h. *Appoint a study manager:* Designate the person responsible for carrying out the study and for analysing and reporting the results.

2.3 Carrying out the study

It is important to carry out the study in a systematic, well-planned manner. If participants are not informed in advance, EDLMs will not be collected at the destination points and the data they contain will be lost. Observe the following rules:

a. *Training:* All study participants must be trained in advance. They must understand the study scope, objectives and procedures, including the retrieval instructions and use of the shipping log. The users must be trained and know how to operate the EDLMs.

b. *Critical control points (CCPs):* Prepare a checklist form which identifies every CCP along the route. The form should provide a place for recording the serial number of the accompanying EDLM, the date and time of each CCP, and the signature of the person responsible for completing the checklist entry. The checklist should accompany the shipment to its final destination. It should be used to record the point of entry and exit from each CCP (for example loading a truck or entering a temperature controlled warehouse); this provides the information needed to link the temperature profile to specific events along the route.[12]

c. *Placing data loggers:* In order to capture actual ambient temperature exposure, attach the EDLM to the outside of the shipper, or place in a well-ventilated box immediately next to the product. Do not pack it in with the product itself.

d. *Designate responsible persons:* The study manager must ensure that a responsible person is designated and fully briefed at each origin point and at each receiving site.

[12] Some EDLMs have an event marker button which can be used to "mark" CCPs on the data record. This provides a useful supplement to a checklist, but cannot replace it.

e. *Distribution schedule:* Send a detailed distribution schedule to each origin and destination site before the study begins. Alert the responsible person in advance of each shipment in order to avoid delays in retrieving the EDLMs and downloading their data.

f. *Log information:* Create a log to record all key information relating to each shipment and for each EDLM used in the study. It is essential to link the serial number of each logger uniquely to each shipment and to provide responsible persons with key shipping information. This includes: the tracking number; shipment date and time; shipping service level, and destination.

g. *Data collection:* The data collection process begins at the study's point of origin. The EDLMs should be programmed to start recording as soon as the product is removed from controlled temperature storage in preparation for shipment. This will ensure that the device records the temperature of the packing environment as well as the length of time required to pack an entire shipment.

2.4 Data retrieval

The EDLMs must be collected and their data downloaded and emailed to the study manager, and analysed as soon as possible. If there are no facilities for downloading at the destination point, the EDLMs themselves should immediately be returned to the study manager. Observe the following steps:

a.. *Data logger retrieval and return:* The responsible person at each receiving site must retrieve the EDLM from the shipment. The device must then be processed as instructed by the study manager and returned to the designated recipient. If required, the means for returning the device – for example a prepaid and addressed envelope – should accompany the EDLM on the outbound journey.

b. *Device calibration:* Ensure that there are valid calibration certificates for all data loggers used in the study. Single-use EDLMs are recommended and these should be supplied complete with the manufacturer's calibration certificate.

c. *Data report and analysis:* Data will be retrieved and analysed to determine temperature statistics for all the loggers used in the study, including:
   - mean temperatures;
   - standard deviations;
   - minimum temperatures;
   - maximum temperatures.

d. *Study errors:* The possibility exists that some data will not be included in the final analysis as a result of routine human error, device failure or other loss. A contingency plan should be defined for such events as:
   - EDLM malfunction;
   - EDLM inadvertently not started/stopped;
   - shipping information is not available for a data logger;
   - loss of EDLM.

2.5 Understanding temperature exposure: the degree-hour concept

If a passive container, loaded with coolant and TTSPP, is exposed to a given ambient temperature outside the labelled temperature range of the product (typically +2.0 °C to +8.0 °C), the natural laws of thermal equilibrium dictate that:

- If the ambient temperature is *above* the maximum recommended transport temperature of the product, the container contents will eventually exceed this upper threshold.
- If the ambient temperature is *below* the minimum recommended transport temperature of the product, the container contents will eventually drop below this lower threshold.

Once either of these thresholds is breached, the TTSPP is at risk of damage.

Passive containers are typically qualified by laboratory tests to establish performance at constant high and low ambient temperatures. However, during real-world transport operations, ambient temperature does not remain constant. As noted above, it can fluctuate widely depending upon the time of day, time of year, height changes, hemispheric crossings along the route (in the case of international transport) and the time spent during loading and offloading.

These fluctuations are captured by following the procedures described in sections 2.1 to 2.4 above. By analysing the collected data, the temperature exposure along different routes, or for different instances of a single route, can then be calculated and compared using the *degree–hour* concept. The principle is straightforward. Ambient temperatures are sampled along the different routes at the same time intervals – for example once every 15 minutes. Each data point is then analysed to establish the extent of the exposure above the upper or lower temperature threshold according to the following formula:

$$E = \sum (T \, x \, t_{dif})$$

Where:

E = temperature exposure in degree–hours;

T = temperature recording interval in hours;

t_{dif} = temperature difference in °C between the threshold temperature and ambient temperature.

Over an entire journey, this formula gives the total degree–hour exposure of the container. This can then be compared with the maximum degree–hour exposure for which the container is qualified.[13] This is the principle adopted for the two methods described in Section 2.6.

2.6 Organizing, analysing and using the data

This section describes how to organize, analyse and use the data. The process of moving from the raw data to a final statistically representative route profile involves a systematic approach to organizing and analysing the collected data and an understanding of simple statistics.

For each shipment, create an Excel® table containing the raw data you have collected – see Table 1. In this simple example, all five journeys are 48 hours long; in reality trip times will vary.

Table 1
Example of an Excel® route profile data table

EDLM interval 0.25 hrs

Elapsed time	Temperature (°C)				
(hours)	Shipment A	Shipment B	Shipment C	Shipment D	Shipment E
0.00	26.7	22.0	22.0	23.9	18.8
0.25	29.1	24.5	22.3	25.2	19.0
0.50	26.8	27.0	22.7	26.2	19.3
0.75	21.6	30.0	22.9	27.1	20.5
..	..	..	..	..	..
47.25	23.4	25.9	14.4	24.1	21.0
47.50	23.3	26.0	19.4	24.4	20.8
47.75	23.5	26.2	21.1	24.2	20.6
48.00	23.6	26.1	19.0	23.9	20.4
Degree hrs	**912**	**957**	**925**	**1040**	**1042**

[13] The degree-hour calculation ignores the effect of solar radiation – a container exposed to the sun may experience a higher effective temperature than the recorded ambient temperature. This radiation effect is also ignored during laboratory testing and is the reason why passive containers should always be kept in the shade.

Organize and analyse the data as follows:

Step 1: Arrange the data by origin and destination.

Step 2: For each location, create a data table in an Excel® spreadsheet containing the following columns:

- elapsed time in hours based on the chosen EDLM data acquisition interval;
- temperature recorded for each shipment at each of the elapsed time intervals.

Step 3: Calculate the degree–hour value for each column using the Excel® formula:

= *EDLM recording interval* * *SUM* (*first data point/last data point*)

Step 4: The column totals indicate the total temperature exposure for five separate shipments in degree–hours above (or below) 0.0 °C and allows these exposures to be compared for severity. In the example in Table 1, shipment E has experienced the greatest exposure and shipment A, the least.

Once step 4 has been completed, there are two alternative ways in which the data can be used. *Method A* uses the collected route profile data to create a statistically robust test profile; this can then be used as a basis for testing proposed packaging solutions under laboratory conditions in a temperature-controlled test chamber. Method B is an empirical rule-of-thumb approach, for use where the performance of the proposed passive container is already known. For example, this method may be used for prequalified cold boxes and vaccine carriers whose cold-life, cool-life and warm-life at constant ambient temperature have been tested and published.[14]

2.6.1 Method A for designing and testing packaging solutions

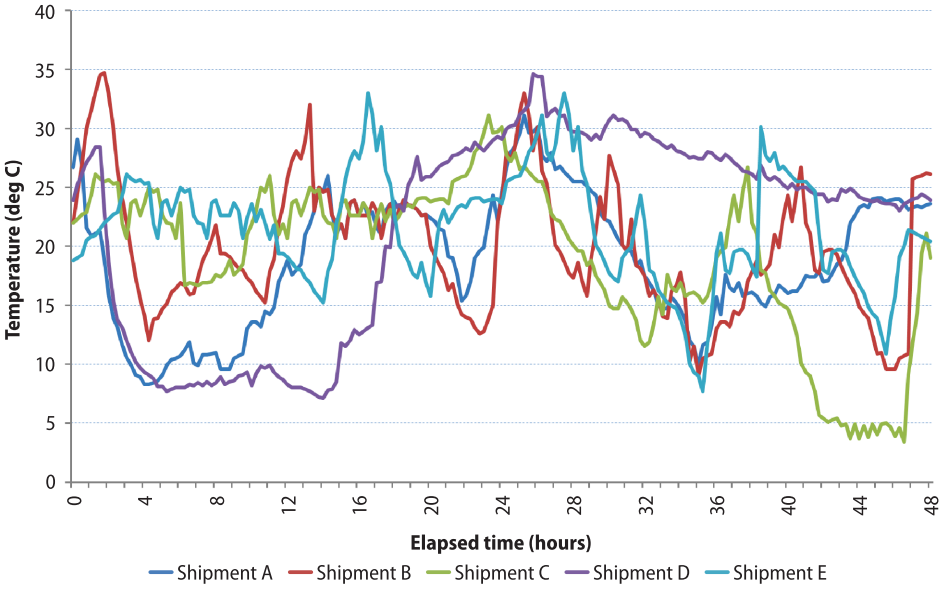
The route profiling data and degree–hour calculations can also be used to derive a test profile; this can then be applied as a basis for conducting the OQ of packaging solutions under laboratory conditions in a temperature-controlled test chamber.

[14] See for example the cold boxes and vaccine carriers in the WHO PQS catalogue (http://apps.who.int/immunization_standards/vaccine_quality/pqs_catalogue/categorylist.aspx).

This section describes how to calculate a test profile, using the data from Table 1 as an illustrative example. In practice a larger data set is needed – as previously noted, a sample size of 30 trips on a given route over the course of a year is considered to be statistically valid. If data on fewer than 30 trips are available for analysis, frequent periodic monitoring can be used to verify the results.

Figure 1 shows the data from Table 1 as a graph. These temperature histories demonstrate why viewing a graph without analysing the data can be very misleading.

Figure 1
Example of a temperature profile graph for five shipments



If we look closely at the five shipment profiles, we can see the following:

- Shipments A and B had similar shipment exposures and similar degree–hour periods (912 and 957).
- Shipment C arrived at its destination around the 40-hour mark but was then put into a refrigerator before the EDLM was switched off at 48 hours. A casual reading of the graph suggests that this shipment had the lowest heat exposure because it spent the lowest and longest period at low ambient temperature. In fact it only had the second-lowest degree–hour exposure (925).

- Shipment D had a very low temperature exposure over the first 15 hours; it was then exposed to very high temperatures from 20 hours onwards. Although this shipment may appear to have been the most exposed it is only the second-worst case (1040 degree hours).
- Shipment E is actually the "worst case" at 1042 degree hours. Even though shipments D and E look very different, they share nearly the same amount of heat under the curve. Graphs can be deceptive.

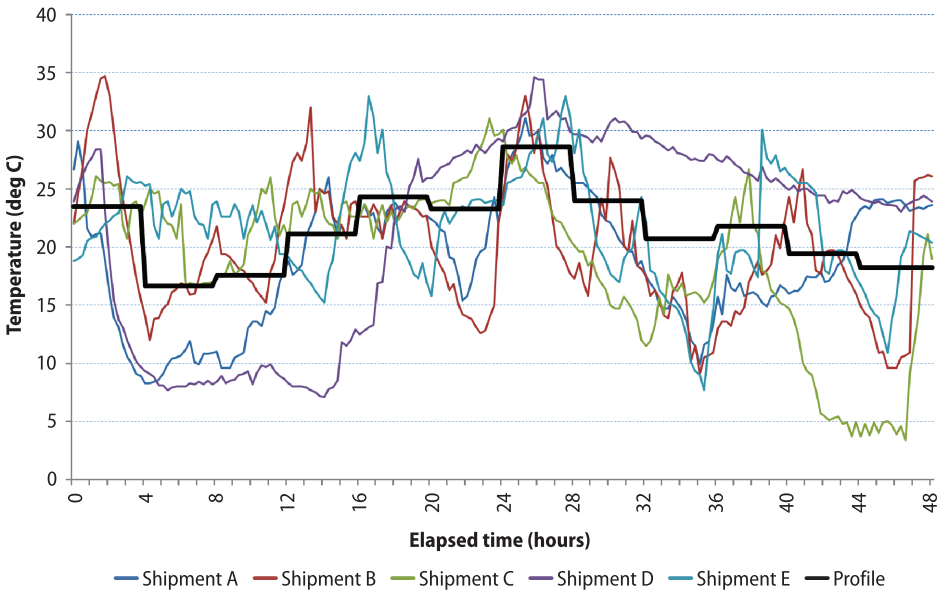
To conduct a laboratory test based on data collected from a set of route profiles, it is necessary to analyse and distil the data into a simplified format which adequately represents the expected temperature exposure of future shipments along the route. This profile can then be used to control the test chamber temperature.

The method illustrated below meets the following objectives:

- The derived profile needs to be in the form of a "step graph". This allows the test chamber thermostat program to be reset at regular intervals.
- The purpose of a step graph is to mimic the typical temperature profile of the route. For example, if the greatest heat exposure occurs at the end of the journey, the step chart must show this. The effect on the package of such variations in the time and extent of exposure cannot be replicated accurately simply by placing the test sample in the test chamber at a constant temperature.
- For practical reasons, the time between temperature changes should be long enough to allow the test chamber to stabilize at each new set point. In practice the intervals should be from one to several hours in duration, depending on the length of the route being simulated.
- The area under the graph should have the same number of degree–hours, or "heat under the curve", as the worst case shipment in the dataset.

Figure 2 shows an example of a test profile derived from a table of EDLM data. The analysis converts the raw data into a simplified step graph with four-hour intervals between steps. In this case, the derived profile which has 1042 degree-hours under the curve – the same as the worst case exposure in the sample of five shipments.

Figure 2
Superimposed step graph. Degree-hours = worst case



Although the step graph appears to ignore some of the temperature extremes, in reality, so long as the profile follows the exposure timeline AND the worst-case degree-hour condition, it should adequately reflect reality.

2.6.2 Method B for passive containers with known performance characteristics

Prequalified passive containers are typically qualified by laboratory testing to establish performance at constant high and low ambient temperatures; for example, WHO prequalified containers are tested at +43.0 °C and −20.0 °C and these performance figures are published.[15]

Once the ambient temperature profile of a transport route is known, these published figures can be used to estimate the *actual* performance of a given container over that specific route – this will nearly always be longer or shorter than the published figure, because ambient temperatures fluctuate.

All passive containers have a finite cold life, cool life or warm life "budget". In a real-life situation, with constantly changing ambient temperatures, the way

[15] See for example the cold boxes and vaccine carriers in the WHO PQS catalogue (http://apps.who.int/immunization_standards/vaccine_quality/pqs_catalogue/categorylist.aspx).

in which this cool life budget is "spent" depends on the actual temperatures that the container experiences:[16]

- When the ambient temperature is on average above +43.0 °C the cool-life budget will be "spent" more quickly than in the laboratory test and cool life will be shorter.
- When ambient temperature is on average less than +43.0 °C the cool-life budget will be "spent" more slowly and cool life will be longer.
- If the ambient temperature remains between 0.0 °C and +20.0 °C the container will keep vaccine below the cool-life threshold permanently.
- If the ambient temperature remains between 0.0 °C and +8.0 °C the container will keep vaccine below the cold-life threshold permanently.
- If the ambient temperature is on average below 0.0 °C, the contents of the container will cool down and eventually drop below 0.0 °C.

If the ambient temperature fluctuations are known (the route profile) the following formula can be used to assess a container's actual performance over that route.

$$E = \sum (h \times t_{dif})$$

Where:

E = total temperature exposure above the threshold temperature, in degree-hours;

h = time increment above the threshold temperature, in hours;

t_{dif} = temperature difference in °C between the threshold temperature and ambient temperature for each increment.

The threshold temperature is selected on the following basis:

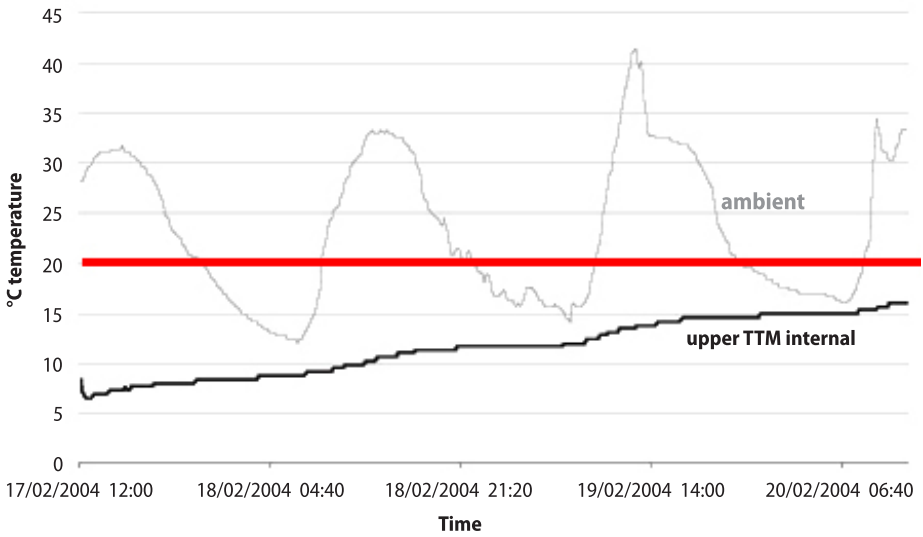
- For cool water-packs, the threshold must not exceed +20.0 °C. A lower temperature (say +15.0 °C) may be chosen if required.
- For frozen and conditioned ice-packs the threshold is normally +8.0 °C.
- For warm water-packs, the threshold is normally 0.0 °C.

Figure 3 shows the temperature profiles inside and outside the container for a monitored shipment in Myanmar, using cool water-packs. The upper line on the graph shows the ambient temperature along the route and the lower line

[16] The temperature thresholds given below are those used for the WHO PQS prequalification tests.

shows the temperature inside the cold box. There were four periods during which the ambient temperature was higher than the +20 °C temperature threshold line. Only during these periods was the temperature inside the cold box being forced above the threshold temperature. In this example, the contents never reached +20 °C, even though the journey lasted nearly 67 hours. The laboratory-tested cool life for the Dometic RCW25 model used for the test is 34.4 hours, only about half that achieved in practice over this route.

Figure 3
Temperature profile in Myanmar



Adapted from: Kartoglu et al. (2009).
Upper TTM internal is the temperature profile in the load.
TTM, time-temperature monitoring device (user-programmable temperature logger).

This example illustrates how route profiling can be used to provide evidence that it is safe to use a specific container for journeys that are longer than the published performance figures. Note that, in a very hot climate, the maximum allowable journey time may be shorter than the published performance figures suggest.

Annex 1 gives worked examples of the use of this method. The route profile data is used to establish whether the degree-hour exposure of the worst-case route profile exceeds the laboratory-tested performance of a proposed passive container, also calculated in degree-hours. This is a two-step operation and there are two cases – a *warm climate* situation where the ambient temperature is consistently above the maximum recommended temperature for transport

of the TTSPP and a *cold climate* situation where the ambient temperature is consistently below the minimum recommended temperature for transport of the TTSPP.

Note: Method B is *not* suitable for use in cases where the ambient temperature fluctuates above and below 0.0 °C. In addition, because it is based on a simple empirical calculation, it is strongly recommended that this method should only be used for in-country transport operations.

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Annex 1

Method B examples

This Annex describes the use of Method B outlined in section 2.6.2 in more detail.

A1.1 Using the data

Systematically collected route profile data can be used to establish whether a specific prequalified container and coolant combination is suitable for a specific route. There are two situations – a *warm climate case* where the ambient temperature along the route is above 0.0 °C and a *cold climate case* where the ambient temperature over the route is generally below 0.0 °C.

Note: The method described below is not suitable where the ambient temperature profile fluctuates more or less equally above and below 0.0 °C AND where conditioned ice-packs or cool water-packs are used to transport freeze-sensitive TTSPPs. Under these circumstances there is a risk that the product may freeze. Such routes should be validated using test shipments where both ambient and load temperatures are monitored.

Section A1.2 describes the calculation method for the warm climate case and section 1.3 describes the method for cold climates.

A1.2. The warm climate case

Figure A1.1 shows four ambient temperature route profiles recorded in a central Asian country. All four examples are for journeys of around 24 hours.

Figure A1.1
Route profile examples

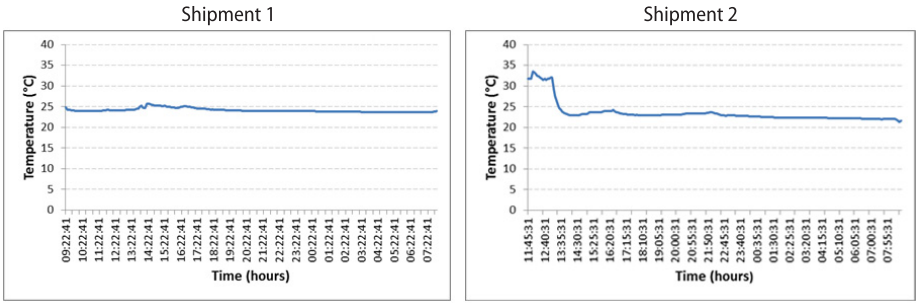
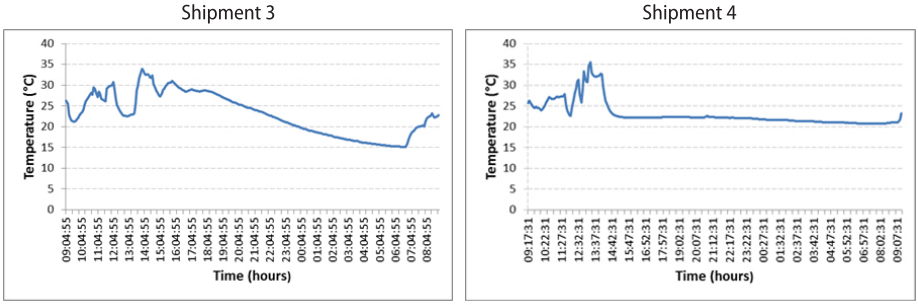


Figure A1.1 *continued*



For each shipment, create an Excel® table containing the raw data you have collected – see Table A1.1.

A1.2.1 Step 1: organize and analyse the route profile data

Organize and analyse the data as follows:

a. Arrange the data sets by origin and destination.
b. For each location, create a data table in an Excel® spreadsheet containing the following columns:
   - Elapsed time in hours based on the selected logger recording interval.
   - Temperature recorded for each shipment after each of the elapsed time intervals.
c. Select the threshold temperature. In this example we will use +20 °C.
d. Calculate the total degree-hour value for each column using the Excel® formula:

   Warm climate case:

   E = SUMIF (first data point/last data point,">threshold temperature\"",*first data point : last data point) * logger interval in hours*)

   The column totals indicate the total temperature exposure for the separate shipments in degree-hours above the chosen threshold temperature and allows these exposures to be compared for severity.

e. Finally, calculate the total journey time for each shipment.

Once the last step has been completed, the data can be used to check the suitability of a proposed prequalified passive container/coolant-pack combination

as described in the next section. Table A1.1 shows part of the data for the four journeys in Figure A1.1.

Table A1.1
Example of an Excel® route profile data table

Recording interval:	**0.25 hours**			
Threshold temperature:	**+20°C**			
Elapsed time	**Temperature (°C)**			
(hours)	Shipment 1	Shipment 2	Shipment 3	Shipment 4
0.00	24.8	31.7	26.2	25.7
0.25	24.2	33.5	22.1	25.1
0.50	24.1	32.5	21.2	24.8
0.75	24.0	31.7	22.1	24.2
1.00	23.9	31.5	23.5	24.7
..	..	..	..	..
23.75			22.8	21.1
24.00				21.8
Degree-hours above 20°C	**547**	**493**	**414**	**557**
Total journey time (hours)	**22.50**	**21.00**	**23.75**	**24.00**

In this example, Shipment 4 received the greatest degree-hour exposure. Shipment 3 received significantly the least, even though the peak temperature rose to nearly 35 °C; the reason for this is that the ambient temperature dropped below the 20 °C threshold for around eight hours. All of the other three profiles remained above the threshold temperature throughout.

A1.2.2 Step 2: assess container suitability

We can now assess whether a given cold box or vaccine carrier is suitable for the four routes, as follows:

a. Vaccine carrier type A has a rated cool life of 12 hours at +43 °C. This can be expressed in another way as a cool life "budget" of $12 \times 43 = 516$ degree-hours.

b. Five hundred and sixteen degree-hours is less than the degree-hour exposure for shipments 1 and 4, but greater than the exposure for shipment 2 and 3. On this basis, the type A container could therefore be used for these last two routes, even though both journey times are nearly twice as long as the rated cool life of the type A container.

A1.3 The cold climate case

The procedure is similar to the warm climate case except that the Excel® formula is slightly different.

A1.3.1 Step 1: organize and analyse the route profile data

Organize and analyse the data as follows:

a. Arrange the data sets by origin and destination.

b. For each location, create a data table in an Excel® spreadsheet containing the following columns:
   - Elapsed time in hours based on the selected logger recording interval.
   - Temperature recorded for each shipment at each of the elapsed time intervals.

c. Calculate the total degree-hour value for each column using the Excel® formula:

   *E = SUMIF (first data point/last data point,"<threshold temperature\"",first data point : last data point) * logger interval in hours*)

   The column totals indicate the total temperature exposure for the separate shipments in degree-hours below the chosen threshold temperature and allow these exposures to be compared for severity.

d Finally, calculate the total journey time for each shipment.

Table A1.2 shows some hypothetical data. Once the last step has been completed, the data can be used to check the suitability of a particular prequalified passive container /warm-pack combination as described in the next section.

Table A1.2
Hypothetical data for a cold climate profile

Recording interval: **0.25 hours**
Threshold temperature: **0°C**

Elapsed time	Temperature (°C)			
(hours)	Shipment 1	Shipment 2	Shipment 3	Shipment 4
0.00	15.00	16.5	15.5	13.5
..	..	..	..	..
23.75			-15.0	-12.5
24.00				-12.8
Degree-hours below 0°C	**-254**	**-338**	**-413**	**-304**
Total journey time (hours)	**22.50**	**21.00**	**23.75**	**24.00**

In this example, shipment 1 has the lowest exposure to sub-zero temperatures and shipment 3 has the highest.

A1.3.2 Step 2: assess container suitability

We can now check whether a proposed passive container has a long enough warm life to be suitable for the routes in the data set:

a. Vaccine carrier type A has a rated warm life of 21.6 hours at −20 °C. This can be expressed in another way as a warm life "budget" of $21.6 \times -20 = -432$ degree-hours.

   The budget of −432 degree-hours is less than the degree-hour exposure for all four shipments. On this basis, the type A container could safely be used on any of the routes.

Revision history

Date	Change summary	Reason for change	Approved

Supplement 15

Temperature and humidity monitoring systems for transport operations

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

Annex 9: Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products

May 2015

Contents

Abbreviations

CI	chemical indicator
ETI	electronic temperature integrator
EDLM	electronic data logging monitor
IATA	International Air Transport Association
NIST	National Institute of Standards and Technology (USA)
PDA	Parenteral Drug Association
TTI	time-temperature integrator
TTSPP	time- and temperature-sensitive pharmaceutical product
URS	user requirements specification

Acknowledgements

The authors of this document are Kevin O'Donnell, Exelsius Cold Chain Management Consultancy and member of the United States Pharmacopeia Expert Committee on Packaging, Storage & Distribution 2010–2015 cycle, Patrick McGrath, Berlinger USA, Dr Umit Kartoglu, WHO Geneva, and Denis Maire, WHO Geneva.

Glossary

3PL: Third-party logistics provider – a firm that provides service to its customers of outsourced (or "third party") logistics services for part, or all of their supply chain management functions.

4PL: Fourth-party logistics provider – a general contractor who manages other 3PLs, truckers, forwarders, custom house agents, and others, essentially taking responsibility for a complete logistics process for the customer.

Ancillary packaging components: Packaging elements used to protect the TTSPP and support or enhance performance of the completed package. This may include retainers, dunnage, secondary protective packaging, and temperature data logging devices.

Chemical indicators: (also called markers or phase-change indicators), are generally impregnated onto a paperboard substrate. These indicators, sometimes referred to as critical temperature indicators, are based on a phase change or chemical reaction that occurs as a function of temperature. Examples include liquid crystals, waxes, polymers, and lacquers that change phase, and thereby their appearance, as a function of temperature. *Threshold type* chemical indicators are irreversible and are suitable for high or low temperatures. Temperature threshold indicators show a response and typically are single-use devices. These indicators provide a signal only when exposed to temperatures higher than (ascending indicator) or lower than (descending indicator) a predetermined threshold temperature. *Progressive type* chemical indicators register multiple events in a cumulative way. As long as the device remains below the threshold temperature no changes occur. However, whenever the threshold temperature is exceeded the reaction is activated and the indicator starts to change. Further temperature violations increase the change process. The indicator for this type of device usually takes the form of a progressive colour change along a paper strip.

Critical control point (CCP): A step or procedure at which controls or checks can be applied to prevent or reduce a hazard or risk to an acceptable or critical level. In the context of distribution and handling of time- and temperature-sensitive health-care products, CCPs are typically defined for those activities where time and temperature abuse may occur or where critical processes that can affect the performance of the packaging solution or containment system are at risk.

Electronic data integrator (EDI): A hybrid electronic instrument intelligently programmed like an *electronic temperature indicator* (ETI) with the report/data producing capabilities of an *electronic data logging monitor* (EDLM) that combines the features and functions of a go/no-go device with the record

retention and data tracking of an EDLM. It uses preprogrammed temperature threshold intelligence to integrate post-analytic functional steps that are typically performed by trained personnel.

Electronic data logging monitor (EDLM): A small portable device that measures and stores temperature at a predetermined time intervals by means of an electronic sensor. They have programmable alarm capabilities, integrated displays, and can create reports and graphs which may be permanently stored, shared and analysed via proprietary hardware, software, desktop application or through hosted databases.

Electronic temperature indicator (ETI): A compact, portable device that measures temperature over time by means of a built-in sensor. They come in a wide range of forms, features, configurations, costs and levels of performance. They have four basic components: a thermistor sensor, a microprocessor, a memory chip, and power source (lithium battery).

Electronic temperature monitoring and event logger system: System for recording and reporting air and/or product temperatures, with optional facilities for recording and reporting specific events such as door-opening or defrost cycles, and for issuing alarms. Such systems may be user-programmable and may also be remotely monitored via a satellite link.

External distribution: Transport of TTSPPs through various steps in the customer's supply chain (i.e. transport from a pharmaceutical manufacturer's distribution centre, to commercial customers (including wholesalers, retailers and buying groups), to clinical facilities or direct to the patient). Contrast with *internal distribution*.

Humidity (relative humidity (RH)): The partial pressure of water vapour in air to the vapour pressure of saturated air at a given temperature. In other words, the RH is the amount of water vapour present, divided by the theoretical amount of moisture that could be held by that volume of air at a given temperature.

Internal distribution: Transport of a TTSPP within a pharmaceutical manufacturer's internal supply chain (i.e. all internal transport from the manufacturing plant to the packaging plant and onwards to warehouses and distribution centres). Contrast with *external distribution*.

Passive systems: Systems which maintain a temperature-controlled environment inside an insulated enclosure, with or without thermostatic regulation, using a finite amount of preconditioned coolant in the form of chilled or frozen gel packs, phase change materials, dry ice or others.

Pharmaceutical product: Any product intended for human use or veterinary product intended for administration to food producing animals, presented in

its finished dosage form, that is subject to control by pharmaceutical legislation in either the exporting or the importing state and includes products for which a prescription is required, products which may be sold to patients without a prescription, biologicals and vaccines. Medical devices are not included.[1]

Qualification: Action of proving that any premises, equipment and supporting systems work correctly and actually lead to the expected results. The meaning of the word *validation* is sometimes extended to incorporate the concept of qualification.

Refrigerated container or reefer: A thermally insulated shipping container or intermodal freight container, equipped with an integrated refrigeration unit, used for the transport of TTSPPs, by road, rail or ocean freight. The refrigeration unit requires an external electrical power supply when located at a land based site, on a container ship or on a quay. During road transport electrical power is typically supplied by a diesel generator.

Refrigerated vehicle: Road transport vehicle such as a van, truck or semi-trailer whose isolated thermostatically controlled cargo compartment is maintained at a temperature different (lower or higher) than the external ambient conditions. The environment inside the cargo compartment may be *temperature-controlled* or *temperature-modified*.

Refrigeration equipment: The term "refrigeration" or "refrigeration equipment" means any equipment whose purpose is to lower air and product temperatures and/or to control relative humidity.

Service level agreement (SLA): A service level agreement or contract is a negotiated agreement between the customer and service provider that defines the common understanding about materials or service quality specifications, responsibilities, guarantees and communication mechanisms. It can either be legally binding, or an information agreement. The SLA may also specify the target and minimum level performance, operation or other service attributes.[2]

Shipping system: All components constituting a completed package including: the outer shipping container, all internal ancillary packaging components and temperature-stabilizing medium.

Storage temperature: The temperature range listed on the TTSPP label, and within the regulatory filings, for long-term storage.

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[1] Definition from WHO/QAS/08.252 Rev 1 Sept 2009. Proposal for revision of WHO good distribution practices for pharmaceutical products – Draft for comments.

[2] Definition from IATA. 2013/2014 Perishable cargo regulations (ePCR) & Temperature control regulations (eTCR).

Temperature excursion: An event in which a TTSPP is exposed to temperatures outside the range(s) prescribed for storage and/or transport. Temperature ranges for storage and transport may be the same or different; they are determined by the product manufacturer, based on stability data.

Temperature stabilizing medium: Ice or gel packs; gel bricks, bottles or pouches; cool water or warm water-packs; phase change materials; dry ice; rapid evaporation media which limit exposure of packed product to excessively high or low temperatures during transport: also referred to as refrigerants or coolants.

Temperature-controlled: Includes any environment in which the temperature is actively or passively controlled at a level different from that of the surrounding environment within precise predefined limits.

Temperature-modified: Includes any environment in which the temperature is predictably maintained at a level different from that of the surrounding environment, but is not actively or passively controlled within precise predefined limits.

Thermistor: An electrical resistor whose resistance is greatly reduced by heating, used for measurement and control.

Time and temperature-sensitive pharmaceutical product (TTSPP): Any pharmaceutical good or product which, when not stored or transported within predefined environmental conditions and/or within predefined time limits, is degraded to the extent that it no longer performs as originally intended.

Time-temperature integrators (TTIs): Are generally chemically impregnated onto a pulp or paperboard substrate. Their reaction rate or diffusion process is used to estimate a temperature equivalent integrated over time. Thus, TTIs provide a measure of accumulated heat rather than instantaneous temperature such as a spike or critical threshold (see *chemical indicators*). The reactions are irreversible – once a colour change, colour development, or diffusion process has taken place, exposure to low temperatures will not restore the indicator to its original state. They change colour, or are marked by a hue progression in intensity (generally from light to dark) in response to cumulative changes in temperature, such as heat, at a rate dependent on the Arrhenius equation. A TTI accumulates all of the temperature conditions experienced by the product to which it is affixed. The colour development can be customized based on the known stability of the product, and in much the same way that most biologicals and pharmaceuticals degrade when exposed to heat – faster at higher temperatures, and slower at lower temperatures.

Transport temperature profile: Anticipated ambient temperature variation and duration to which a TTSPP may be exposed during transport.

User requirement specification (URS): The attributes assigned by the user in advance of a qualification test to establish minimum performance limits. Sometimes referred to as a *functional requirements document*.

Validation: Documented testing performed under highly controlled conditions, demonstrating that processes, methods, and systems consistently produce results meeting predetermined acceptance criteria.[3]

[3] Parenteral Drug Association (PDA) Technical Report No. 39: Guidance for temperature controlled medicinal products: Maintaining the quality of temperature-sensitive medicinal products through the transportation environment, 2007.

1. Introduction

This technical supplement has been written to amplify the recommendations given in section 6.5 and section 9 of WHO Technical Report Series No. 961, 2011, Annex 9: *Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products*.[4]

The strength, efficacy, and potency of a pharmaceutical product can be profoundly degraded by changes in temperature. Some products may also be affected by exposure to adverse humidity levels.[5] It is not always possible completely to prevent degradation during transport, but damage can be minimized through good handling and storage practices, by qualifying the mode and route of transport, and by using qualified packaging.

For quality assurance purposes, stakeholders in the supply chain should be able to supply documentary evidence that the pharmaceutical product has not exceeded the acceptable limits of time, temperature and humidity exposure, as determined by the manufacturer's stability data for the product. This evidence is supplied by recording devices and technologies that provide a history of temperature and/or humidity to which the product was exposed during transport and external distribution. It is important to bear in mind that humidity can only be *measured* during transport; it cannot generally be *controlled*.

Effective temperature and humidity monitoring is an important component of good distribution practice (GDP) and can only be achieved if close attention is paid to the relevant critical control points (CCPs).

The following Technical Supplements are also relevant:

- *Qualification of temperature-controlled road vehicles*
- *Qualification of shipping containers*
- *Transport route profiling qualification*
- *Temperature-controlled transport operations*
- *Temperature and humidity monitoring systems for fixed storage areas.*

1.1 Requirements

Generally speaking, the shipper is responsible for ensuring product temperature compliance during transport. Shippers should operate under the terms of a formal service level agreement (SLA) with their carrier(s) or logistics service

[4] http://apps.who.int/medicinedocs/documents/s18683en/s18683en.pdf

[5] Note that it is generally considered that humidity exposure has a minimal effect on pharmaceutical products that are in their original manufacturer's packaging and further enclosed in an active or passive shipping container. However, there may be some products for which this is an important consideration. Card packaging and primary container labels can also be degraded by high levels of humidity.

provider(s) i.e. freight-forwarder, third-party logistics provider (3PL), fourth-party logistics provider (4PL) or integrator. If shipping operations are carried out in-house, they should be controlled by a comprehensive set of standard operating procedures (SOPs).

SLAs and SOPs must clearly specify the types of temperature and humidity monitoring device that are to be used, when and where they are to be installed, and how the data they generate should be collected, reported and stored.

1.2 Objectives

The objective of this Technical Supplement is to provide:

- A technical description of the device technologies used to record temperature and humidity exposure during the transport life-cycle of a pharmaceutical product.
- A description of the documentary evidence that should be supplied to regulatory authorities and other interested parties so that quality assurance and regulatory compliance can be demonstrated and maintained.

1.3 Target readership

This supplement is intended for all those responsible for the transport of TTSPPs from one fixed storage point to another in the supply chain. The target readership also includes those responsible for providing evidence of temperature and humidity exposure during this process. Monitoring temperatures in fixed storage locations is covered by the companion Technical Supplement: *Temperature and humidity monitoring systems for fixed storage areas*.

Staff responsible for transport operations need to have a good knowledge of the various types of temperature and humidity monitoring device used in the transport environment, together with their strengths, weaknesses and appropriate uses. They must also be capable of operating, reading and interpreting data from these devices and must be familiar with, and follow, good documentation practice.

2. Guidance

Temperature control during air, ocean or ground transport can be maintained using either active or passive shipping systems. These systems are fully described in the companion Technical Supplement: *Temperature-controlled transport operations*; this supplement covers product packing, distribution and product off-loading for the following system types:

- refrigerated and temperature-controlled vehicles;
- passive shipping systems;
- active shipping systems for air transport; and:
- active shipping systems for ocean transport.

The guidance below focuses on the selection and use of suitable temperature monitoring devices for different legs (or stages) of the transport operation.

2.1 Associated materials and equipment

The key physical components of a quality-assured temperature-controlled transport system are the active and passive packaging systems in which products are placed during transport and the monitoring devices used to record temperature and humidity exposure within these packaging systems. The specific characteristics of the operational environments where these monitoring devices are used are described in the companion Technical Supplement: *Temperature-controlled transport operations*.

2.2 Temperature- and humidity-monitoring devices

The main reason for choosing a temperature- or humidity-monitoring device is to determine whether or not the quality of a pharmaceutical product has potentially been compromised as a result of exposure to harmful or unwanted conditions. The type of technology and the device selected should be based on a URS.

Depending on the purpose defined in the URS, the selected device may serve as:

- a device for determining acceptance or rejection of a shipment;
- a post-use analytical tool for identifying weakness in the transport system, for carrying out a trend analysis, or for collecting performance data.

The level of detail provided by the available range of devices varies widely and is dependent on the specific application and the technology used. This is a field which is undergoing rapid technological development.

All monitoring systems must meet regulatory expectations and requirements and must provide the evidence needed to demonstrate that the TTSPP has not been exposed to adverse temperatures during storage or transport. When specified to do so, the system must also be able to provide the temperature records needed for documentation purposes.

Single-use devices should be supplied with a manufacturer's calibration certificate and the certificate should cover the entire temperature range over which the device is designed to be used. These devices cannot be recalibrated. Multiple use devices should be calibrated against a certified, traceable reference standard once a year, unless otherwise justified. Calibration should demonstrate the accuracy of the unit across the entire temperature range over which the device is designed to be used.

Whenever devices are selected it is essential to consider the needs of the specific application, including ease of use and ease of integration throughout the supply chain. Some devices require additional software or hardware, such as a docking station; this may not be acceptable in certain cases. Whatever device or system is chosen, it should be accurate, stable, reliable and validated.

2.2.1 Device types

The glossary gives a full definition of each of the temperature-monitoring devices listed below. Some of the more sophisticated electronic devices include humidity data collection. However, it is generally considered that humidity exposure has a minimal adverse effect on pharmaceutical products when they are in hermetically sealed primary packaging and further enclosed in an active or passive shipping container.

Figure 1 shows examples of the following commonly used device types and Table 1 itemizes their features, benefits, limitations and proposed applications:

- chemical indicators (CIs), both threshold and progressive types, and chemical time-temperature integrators (CTTIs);
- electronic temperature indicators (ETIs);
- electronic data logging monitors (EDLMs);
- electronic data integrators (EDIs);
- electronic temperature monitoring and event logger systems for refrigerated vehicles (TMEL).

The accuracy and level of performance of these devices varies between manufacturers and they should therefore be carefully selected to meet the specific URS.

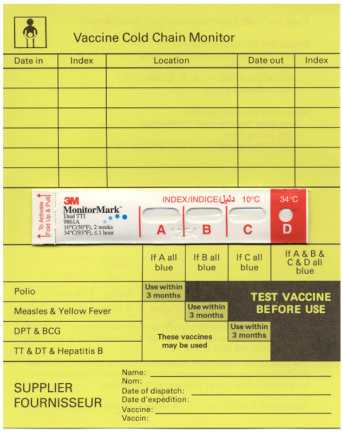
Figure 1
Examples of device types

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

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

CI: Temptime FREEZEmarker®

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



CTTI: Vaccine vial monitor

Electronic temperature indicators (ETI)

Sensitech FreezeAlert™

Berlinger Q-tag® Quad

LogTag TICT-iS0°Tag®

Figure 1 *continued*

Electronic data logging monitors (EDLM)

Libero data logger

LogTag® TRIX-8 Temperature Recorder

Electronic data integrators (EDI)

Berlinger Q-tag® CLm Doc

LogTag® TIC20

VaxAlert™ Temperature Indicator

Electronic temperature monitoring and event logger systems (TMEL)

Transcan Sentinel with thermal printer

Table 1
Performance characteristics of monitoring devices

		Portable						Fixed
		CI		CTTI	ETI	EDLM	EDI	TMEL
		TCI	PCI					
Features and benefits	Provides go / no-go information at a glance	✓			✓			
	Responds when a temperature threshold has been exceeded	✓	✓		✓			
	Responds to a single event	✓			✓			
	Irreversible change	✓	✓	✓	✓			
	Responds to a temperature equivalent integrated over time			✓				
	Responds as a result of a single and cumulative events		✓	✓				
	Response occurs as a result of cumulative exposure		✓	✓				
	Visual indication: Color change, colour development, diffusion, graphical indication	✓	✓	✓	✓			
	No additional equipment needed to read results	✓	✓	✓	✓	[1]	[1]	[1]
	Accuracy of ±0.5 °C				✓	✓	✓	✓
	Multiple temperature alarm threshold capabilities				✓	✓	✓	✓
	Multiple time alarm threshold capabilities				✓	✓	✓	✓
	Alarm parameters programmable by manufacturer only	✓	✓	✓	✓			
	Alarm parameters programmable by manufacturer or user					✓	✓	✓
	Can be used as an analytical tool			✓		✓	✓	✓
	Capable of producing graphs, numerical data and summary reports				[2]	✓	✓	✓

Table 1 *continued*

		Portable						Fixed
		CI		CTTI	ETI	EDLM	EDI	TMEL
		TCI	PCI					
	Single use devices are calibrated by manufacturer prior to use				✓		✓	
	Devices are individually serialized for traceability	✓ [3]	✓ [3]	✓ [3]	✓	✓	✓	✓
	User activation required		✓		✓	✓	✓	✓
	User deactivation required					✓	✓	✓
Limitations	Accidental activation may occur if not properly stored/transported prior to use	✓ [4]						
	Monitoring upper and lower limits at the same time requires use of two indicators	✓	✓	✓				
	Interpretation of colour change may be affected by human factors		✓	✓				
	Not an analytical tool	✓	✓		✓			
	Standard time and temperature limits (some customization available for high volume applications)	✓		✓	✓		✓	
	Single use device	✓	✓	✓	✓			
	No time-specific traceability	✓	✓	✓	✓			
	Requires regular calibration					✓	✓ [5]	✓
	Temperature accuracy varies over operating range				✓	✓	✓	✓
	Recording frequency and recording time tied to size of device memory					✓		✓
	Additional proprietary hardware, software application or licensing may be required for downloading data				[2]	✓	✓	
	12-36 month battery life			✓ [6]	✓	✓	✓	
	Requires professional installation							✓

Table 1 *continued*

		Portable						Fixed
		CI		CTTI	ETI	EDLM	EDI	TMEL
		TCI	PCI					
Useage	Point-to-point distribution	✓	✓		✓	✓	✓	✓
	Entire life-cycle of pharmaceutical product			✓				

Key: CI: chemical indicator; TCI: threshold chemical indicator; PCI: progressive chemical indicator; CTTI: chemical time temperature integrators; ETI: electronic temperature indicator; EDLM: electronic data logging monitor; EDI: electronic data integrator; TMEL: electronic temperature monitoring and event logger system.

[1] Some versions of these devices hace LCD screens where results can be read. However, for download, additional equipment may be needed.

[2] Some versions of these devices are downloadable and produce both graphs and detailed data sheets.

[3] These devices are serialized by lot, not individually.

[4] If devices are incorrectly packed during shipment from the supplier, the START button on some electronic devices may inadvertently trigger activation. This is uncommon.

[5] Applies only to multiple use devices.

[6] Some devices have 5 year battery life.

2.2.2 Data collection, storage and retrieval

Different devices generate different types and amounts of information. Devices, such as EDLMs, that record time and temperature data that can be downloaded must be used to produce this information in accordance with the relevant regulatory requirements for documented data storage.

In most instances, downloaded time and temperature data should be retained for at least three years in a non-volatile format that enables the data to be retrieved. Suitable formats include printed hard copies or a non-volatile and retrievable electronic medium such as a computer hard drive, tape drive, flash drive or DVD. Storage in a secure web-based data repository may also be acceptable.

Go/no go data of the type supplied by CIs, CTTIs and ETIs should be recorded on the appropriate product arrival report and this information should be used to make decisions on whether to accept the TTSPP consignment into active storage at the receiving store, or whether to quarantine it until an investigation has taken place and a final disposition has been made.

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Revision history

Date	Change summary	Reason for change	Approved

Supplement 16

Environmental management of refrigeration equipment

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

Annex 9: Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products

May 2015

Contents

Abbreviations

A2L	An ASHRAE flammability class
ASHRAE	American Society of Heating, Refrigerating and Air-Conditioning Engineers
ATP	Agreement on the International Carriage of Perishable Foodstuffs and on the Special Equipment to be Used for such Carriage
BS EN	British Standard European Norm
CFC	chlorofluorocarbons
EN 378	European Norm (standard) on the safety of refrigerants
F-Gas	fluorinated gas
GWP	global warming potential
HC	hydrocarbon
HCFC	hydrochlorofluorocarbon
HFC	hydrofluorocarbon
HFO	hydrofluoro-olefin
MOP-19	Nineteenth Meeting of the Parties to the Montreal Protocol
ODP	ozone depletion potential
ODS	ozone depleting substance
SOP	standard operating procedure
TEWI	total equivalent warming impact
TTSPP	time- and temperature-sensitive pharmaceutical product
UNECE	United Nations Economic Commission for Europe
UNEP	United Nations Environment Programme

Acknowledgements

The author of this document is Richard Lawton, Technical Director, Cambridge Refrigeration Technology, Cambridge, England.

Glossary

Article 5 country: The main objective of the Multilateral Fund for the Implementation of the Montreal Protocol is to assist developing country parties to the Montreal Protocol whose annual per capita consumption and production of ozone-depleting substances (ODS) is less than 0.3 kg to comply with the control measures of the Protocol. Currently, 147 of the 196 parties to the Montreal Protocol meet these criteria (they are referred to as Article 5 countries).

Non-Article 5 country: Parties to the Montreal Protocol that have an ODS consumption of greater than 0.3 kg per capita on the date of entry of the Montreal Protocol, or at any time thereafter within 10 years of the date of entry into force of the Protocol.

Pharmaceutical product: Any product intended for human use or veterinary product intended for administration to food producing animals, presented in its finished dosage form, that is subject to control by pharmaceutical legislation in either the exporting or the importing state and includes products for which a prescription is required, products which may be sold to patients without a prescription, biologicals and vaccines. Medical devices are not included.[1]

Refrigeration equipment: The term "refrigeration" or "refrigeration equipment" means any equipment whose purpose is to lower air and product temperatures and/or to control relative humidity.

Service level agreement (SLA): A service level agreement or contract is a negotiated agreement between the customer and service provider that defines the common understanding about materials or service quality specifications, responsibilities, guarantees and communication mechanisms. It can either be legally binding, or an information agreement. The SLA may also specify the target and minimum level performance, operation or other service attributes.[2]

Standard operating procedure (SOP): A set of instructions having the force of a directive, covering those features of operations that lend themselves to a definite or standardized procedure without loss of effectiveness. Standard operating policies and procedures can be effective catalysts to drive performance improvement and improve organizational results.

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[1] Definition from WHO/QAS/08.252 Rev 1 Sept 2009. Proposal for revision of WHO good distribution practices for pharmaceutical products – Draft for comments.

[2] Definition from International Air Transport Association (IATA). 2013/2014 Perishable cargo regulations (ePCR) and Temperature control regulations (eTCR).

Third party accreditation: Accreditation or certification by an organization that issues credentials or certifies third parties against official standards as a means of establishing that a contractor is competent to undertake a specific type of work. Third-party accreditation organizations are themselves formally accredited by accreditation bodies; hence they are sometimes known as "accredited certification bodies". The accreditation process ensures that their certification practices are acceptable, typically meaning that they are competent to test and certify third parties, behave ethically and employ suitable quality assurance.

Time and temperature-sensitive pharmaceutical product (TTSPP): Any pharmaceutical good or product which, when not stored or transported within predefined environmental conditions and/or within predefined time limits, is degraded to the extent that it no longer performs as originally intended.

1. Introduction

This technical supplement has been written to amplify the recommendations given in section 10.2 of WHO Technical Report Series No. 961, 2011, Annex 9: *Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products*.[3] It gives guidance on the selection of refrigerant gases and blowing agents so that countries can minimize the environmental impact of cold chain equipment used in fixed storage and transport operations. Related topics are covered in the Technical Supplement: *Maintenance of refrigeration equipment*.

1.1 Requirements

Ensure that all new refrigeration equipment for temperature-controlled storage and transport is specified to:

- use refrigerants that comply with the Montreal Protocol;
- minimize or eliminate the use of refrigerants with high global warming potential (GWP), and;
- minimize carbon dioxide (CO_2) emissions during operation.

Select equipment to minimize whole-life environmental impact and employ best practice to eliminate leakage of refrigerant into the environment during installation, maintenance and decommissioning of refrigeration equipment.

Follow standard operating procedures (SOPs) for purchase, maintenance and end of equipment life disposal, and ensure compliance with international protocols and accords on climate change and environmental protection. Train staff to avoid excessive release of refrigerants.

1.2 Objectives

The objectives of this Technical Supplement are to provide guidance on how to meet the above requirements with regard to the environmental impact of fixed and mobile refrigeration equipment, while ensuring the efficacy of TTSPP storage and transportation.

[3] http://apps.who.int/medicinedocs/documents/s18683en/s18683en.pdf

1.3 Target readership

The target audience is principally the owners and operators of warehouses, pharmacies and other stores and owners and operators of refrigerated vehicles used to transport TTSPPs. Some of the content may also be useful to equipment manufacturers and suppliers.

2. Guidance

The component elements of refrigeration systems contain gases which can cause long-term environmental damage; some products may also be toxic or flammable. The principal focus of this Technical Supplement is to prevent these gases from leaking into the atmosphere where they accumulate, or into the immediate environment where they may affect occupants or become a fire hazard.

Refrigerant gases containing chlorine or bromine have a high ozone depletion potential (ODP) and damage the planet's ozone layer. These and several other gases also have a high global warming potential (GWP) and contribute disproportionately to the continuing increase in global warming.

The principal focus of the environmental impact is the refrigeration source and the prime mover. However, the thermal performance of cold room and refrigerator insulation and the insulation of the bodies of refrigerated vehicles also have an impact. Insulation limits heat transmission. This reduces the size and refrigerant charge needed for the cooling machinery, reduces energy consumption and hence limits CO_2 emissions from the refrigeration plant. However, the blowing agents used to manufacture many insulation products may have a high ODP and/or high GWP. Leakage of these agents into the atmosphere during the service life of the equipment and during end of life disposal can therefore have an adverse environmental impact.

2.1 Associated materials and equipment

Minimizing the emission of gases with high GWP requires rigorous service procedures and appropriate service equipment. Service equipment includes refrigerant recovery machines, refrigerant recovery bottles and leak detectors.

2.2 Montreal Protocol

Use of refrigerant gases and blowing agents is governed by the Montreal Protocol on Substances that Deplete the Ozone Layer. This Protocol was subsequently adjusted and/or amended in London in 1990, Copenhagen in 1992, Vienna in 1995, Montreal in 1997 and Beijing in 1999.

Under the amendments and adjustments to the Protocol, non-Article 5 parties (see **Annex 1**) were required to phase out production and consumption of: halons by 1994; chlorofluorocarbons (CFCs), carbon tetrachloride, hydrobromochlorofluorocarbons and methyl chloroform by 1996; bromochloromethane by 2002; and methyl bromide by 2005. Article 5 parties were required to phase out production and consumption of hydrobromochlorofluorocarbons by 1996, bromochloromethane by 2002, and CFCs, halons and carbon tetrachloride by 2010. Article 5 parties must still phase

out production and consumption of methyl chloroform and methyl bromide by 2015. Under the accelerated phase-out of hydrochlorofluorocarbons (HCFCs) adopted at the Nineteenth Meeting of the Parties to the Montreal Protocol (MOP 19), HCFC production and consumption by non-Article 5 parties was frozen in 2004 and is to be phased out by 2020, while for Article 5 parties, HCFC production and consumption was to be frozen by 2013 and phased out by 2030 (with interim targets prior to those dates, starting in 2015). There are exemptions to these phase-outs to allow for certain uses for which feasible alternatives are lacking.

2.3 Selection of refrigerants and blowing agents

A numbering system is used for refrigerants (e.g. R-134a), developed by the American Society of Heating, Refrigerating and Air-Conditioning Engineers (ASHRAE). Prefixes can be: R, CFC, HCFC, HFC or HFO. The rightmost numeric value indicates the number of fluorine atoms in the molecule, the next value to the left is the number of hydrogen atoms plus 1, and the next value to the left is the number of carbon atoms less one (zeroes are not stated). The remaining atoms are chlorine.

2.3.1 Use of chlorofluorocarbons (CFCs)

A CFC is an organic compound that contains only carbon, chlorine, and fluorine, produced as a substituted derivative of methane and ethane. It is an ozone-depleting compound, which is highly damaging to the environment.

It is now illegal to operate refrigerated vehicles using CFCs as the refrigerating fluid or to have CFCs within the insulation in non-Article 5 countries. WHO recommends that fixed refrigeration equipment and refrigerated vehicles containing CFC's should not be purchased or operated.

2.3.2 Use of hydrochlorofluorocarbons (HCFCs)

HCFCs are similar to CFCs but contain hydrogen and have a lower ozone-depleting potential.

It is now illegal to purchase new refrigerated vehicles that use HCFCs as the refrigerating fluid or that have HCFCs within the insulation in non-Article 5 countries, although they can still be operated using recycled refrigerant. It is recommended that refrigerated vehicles containing HCFCs should not be purchased in Article 5 countries although they can and should be operated until the end of their design life.

2.3.3 Use of hydrofluorocarbons (HFCs)

HFC refrigerants are composed of hydrogen, fluorine and carbon atoms connected by single bonds; they do not deplete the ozone layer because they do

not contain chlorine or bromine. However, they do have a high GWP; some higher than others. Atmospheric concentrations of these gases are rapidly increasing.

Currently most refrigerated transport solutions and most fixed refrigeration equipment depend on the use of HFCs and there is no alternative; however HFCs with lower GWP should be considered. Hydrocarbons are recommended for smaller systems.

2.3.4 Use of hydrofluoroolefin (HFO)

HFO (hydrofluoroolefin) refrigerants are the fourth generation of fluorine-based refrigerants. HFO refrigerants are composed of hydrogen, fluorine and carbon atoms, but contain at least one double bond between the carbon atoms.

These compounds have zero ODP and a very low GWP. Therefore these products offer a more environmentally friendly alternative, although there are issues with flammability.

At the time of writing, these products are in an early stage of development but are beginning to be introduced into the market. When available they would be an acceptable alternative, providing machinery is correctly designed to take into account their flammability.

2.3.5 Use of hydrocarbons (HCs)

Several hydrocarbons (HCs) have excellent refrigeration fluid properties, zero ODP, and very low GWP. The sole disadvantage of using HCs is their flammability and the risk of explosion. It is recommended that small refrigerators with refrigerant charges of less than 150 g should be preferentially purchased where an option to do so exists. Larger charges can be used, provided safety conditions are met.

The limiting factor associated with the use of HC refrigerants is the refrigerant charge size, the occupancy category and the room size. Systems with charge sizes of 0.15 kg or less may be installed in a room of any size. However, for systems with charge size of more than 0.15 kg and up to 1.5 kg, the room size should be such that a sudden loss of refrigerant does not raise the mean gas concentration in the room above the practical limit 0.008 kg/m^3. If it is proposed to use even large charges of HC, this is permitted although it is strongly recommended that European Norm (standard) EN 378 on the safety of refrigerants be consulted for safety recommendations.

2.3.6 Ammonia and carbon dioxide

Ammonia has excellent refrigerant properties and has been used for many years in larger cold stores. It is still widely used in gas and kerosene-fuelled absorption refrigerators and freezers, which provide cold chain in places without a reliable electrical supply. Ammonia is inexpensive and leaks can easily be detected by

smell, it has no ODP and low GWP. Its disadvantages are that it has moderate flammability and is toxic.

Carbon dioxide (CO_2) could well be the refrigerant of the future. It has mostly good thermodynamic properties and it is starting to be used in supermarket, cold store and bottle cooler applications. It has no ODP and a GWP, by definition, of 1. Its main disadvantages are high operating pressures and a critical point (inability to condense) of 29 °C, which makes it operate less efficiently, transcritically, in hot environments.

2.3.7 Other cooling technologies

Other technologies for cooling exist that do not, in themselves, have ODP but are less common than vapour compression and absorption systems. However all passive systems such as liquid nitrogen, ice-packs and phase change material (PCM)-packs rely on a source of mechanical cooling using one of the gases described above. Examples include:

- *Liquid nitrogen:* used for cooling in some countries.
- *Liquid or dry CO_2:* liquid CO_2 is used for cooling refrigerated vehicles in some countries. Solid carbon dioxide (dry ice) is used to keep small packs cool.
- *Water-packs:* Water-based coolant-packs may either be frozen (ice-packs) or cooled (cool water-packs). They are placed in insulated containers to help maintain the temperature of the stored product.
- *PCMs:* these are coolant-packs containing waxes or other substances that are pre-cooled and placed in insulated containers like water-packs. PCMs have the specific advantage that they can be designed to change phase at a desired temperature – e.g. +5 °C.
- *Peltier effect:* Peltier cooling is an electronic system that can be used to maintain the temperature of small cool boxes.

2.4 Counterfeit refrigerants

A problem with counterfeit refrigerants has emerged in recent years in response to the restrictions put in place by the Montreal Protocol. These refrigerants are labelled as pure HFCs or HFC mixtures but in fact contain a cocktail of refrigerants including those with an ODP. Some counterfeit blends contain methyl chloride, which is toxic and can react with aluminium components, sometimes causing explosions. Counterfeit refrigerants usually contain chlorine; they are cheaper than might be expected and do not come through recognized supply channels. Refrigerants containing chlorine can be detected using a flame halide torch.

2.5 Thermal insulation

Foam insulation in cold store panels, refrigerator casings and refrigerated vehicle bodies has a considerable environmental impact. The insulation foam is expanded with a reagent that can have a GWP or ODP and the efficacy of the insulation affects the fuel consumption of the refrigeration equipment. Insulation also ages and can deteriorate by around 5% each year. As the foam deteriorates, the blowing agent leaches away; this adds to GWP and gives rise to additional fuel and electricity consumption.

2.6 CO_2 emissions

CO_2 emissions from the prime mover driving the refrigeration equipment are affected by the efficacy of the insulation and contribute to GWP via the total equivalent warming impact (TEWI). The more work the refrigeration system does, the more energy is consumed and therefore the higher the CO_2 emissions. The regulations of the Agreement on the International Carriage of Perishable Foodstuffs and on the Special Equipment to be Used for such Carriage (ATP regulations) for frozen transport state that the insulation should have a value of <0.4 W/m²K and for chilled transport a value of <0.7 W/m²K. It is recommended that new vehicles be selected with an insulation coefficient <0.4 W/m²K.

2.6.1 Kyoto Protocol

The Kyoto Protocol to the United Nations Framework Convention on Climate Change is an international treaty that is supposed to set binding obligations on industrialized countries to reduce emissions of GWP (greenhouse) gases. While all countries agree that GWP affects the climate, there is disagreement about accepting all of the reduction implications and therefore some countries have not signed or ratified the agreement. Nevertheless, responsible operators of fixed and mobile refrigeration equipment should take steps to minimize energy consumption and GWP gas emissions. This is also likely to be in their own long-term economic interest, because of the savings in operational cost from using more efficient equipment.

2.6.2 CO_2 emissions from prime mover

The size of the refrigeration equipment relative to the heat load has a significant effect on CO_2 emissions. The ATP agreement stipulates an over-capacity of a least 1.75 times the overall heat ingress into the insulated body under operating conditions and +30 °C ambient temperature. If the predicted ambient temperature is above +30 °C, it would be prudent to increase the over-capacity to 2.25.

2.6.3 ODP and high GWP refrigerants

When selecting fixed refrigeration systems and refrigerated vehicles, those involved in the procurement procedure should consider the ODP and GWP of the refrigerating fluid used in the cooling equipment and the blowing agent in the insulating foam. Table 1 gives the ODP and GWP of popular refrigerating fluids used in refrigeration systems. When specifying new equipment, the table can be used to help select reagents with zero ODP and the lowest technically possible GWP.

Table 1
ODP and GWP of common refrigerants and blowing agents

Refrigerant	Name	Structure	GWP	ODP
CFC-11	trichlorofluoromethane	CCl_3F	4 750	1
CFC-12	dichlorodifluoromethane	CCl_2F_2	10 900	1
CFC-502	chlorodifluoromethane chloropentafluoroethane	$CHClF_2$ $CClF_2CF_3$	4 657	0.25
HCFC-141b	1,1-dichloro-1-fluoroethane	CCl_2FCH_2	725	0.12
HCFC-22	chlorodifluoromethane	$CHClF_2$	1 810	0.05
HFC-134a	1,1,1,2-tetrafluoroethane	CH_2FCF_3	1 430	0
HFC-404a	pentafluoroethane 1,1,1-trifluoroethane 1,1,1,2-tetrafluoroethane	CHF_2CF_3 CH_3CF_3 CH_2FCF_3	3 922	0
HFC-407a	difluoromethane pentafluoroethane 1,1,1,2-tetrafluoroethane	CH_2F_2 CHF_2CF_3 CH_2FCF_3	2 107	0
HFC-410a	difluoromethane pentafluoroethane	CH_2F_2 CHF_2CF_3	2 088	0
HFO-1234yf	2,3,3,3-tetrafluoropropene	$CF_3CF{=}CH_2$	4	0
HFO-1234ze	trans-1,3,3,3-tetrafluoropropene	$CF_3CH{=}CHF$	6	0
N/A	cyclopentane	C_5H_{10}	11	0
HC-290	propane	$CH_3CH_2CH_3$	11	0
HC-600s	isobutane	$CH(CH_3)_2CH_3$	3	0
R-717	ammonia	NH_3	0	0
R-744	carbon dioxide	CO_2	1	0

CFC-11 and HCFC-141b were previously used as insulation foam blowing agents. These gases have now been mostly replaced with cyclopentane, although various HFCs are sometimes used. First-generation CFC refrigerants, such as CFC-12 and CFC-502, are no longer used. HCFC-22, and blends containing this gas, have a lower ODP and are now used less frequently; they are illegal in non-Article 5 countries. HFC-134a and HFC-404a are commonly used refrigerants. However, there is now pressure on HFC-404a because of its high GWP and alternatives are being sought. HFOs are the new generation of refrigerants currently under development, but these have flammability concerns in the form of "slow flame propagation"; they are classed by ASHRAE as A2L, low toxicity, low flammability refrigerants with a maximum burning velocity of ≤ 10 cm/s. Ammonia has been used for many years in large stores; CO_2 is now used in larger equipment and in development models of refrigerators and transport units.

2.7 Installation and maintenance

Only technicians trained in handling refrigerant gases should carry out the installation and maintenance of refrigeration equipment.

Historically, vehicle-cooling systems have high levels of gradual leakage from mechanical seals, glands, valves and mechanical joints. Generally, fixed equipment has lower leakage rates.

Regular leakage checks can identify such leaks and minimize emissions. An inventory should be maintained and an associated SOP detailing the following:

- quantity and type of refrigerant charge in each piece of equipment;
- quantities of refrigerant added at service;
- quantities of refrigerant recovered in service;
- dates and results of leakage checks;
- identity of personnel undertaking checks.

2.8 Decommissioning

At the end of its economic life, fixed refrigeration equipment and refrigerated vehicles need to be decommissioned. The life of a vehicle is likely to depend on the condition of the insulated body, although it is unlikely to be in excess of 15 years, and more likely 12 years.

The following is recommended:

- A trained technician should remove the refrigerant from the cooling equipment. It should be incinerated in an approved plant or recycled by a refrigerant manufacturer with appropriate facilities.

- The insulated enclosure, if it is to be used as a store, should be made safe to ensure it is impossible for people to get trapped inside.
- If the insulation of the enclosure contains ODP or GWP reagents, it should, if technically feasible, be crushed so that the foaming reagents can be recovered.
- Absorption refrigerators should be disposed of with care as they are pressurized and older units contain a corrosion inhibitor (sodium dichromate). Some countries restrict the disposal of this substance in landfill.

2.9 Staff training

All employees who are involved with the handling of refrigerants should be given training. This should include:

- handling of refrigerant fluids;
- installation;
- maintenance;
- servicing.

Training should also include reference to the environmental impact of releasing high GWP refrigerants into the environment and their effect in accelerating climate change.

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[4] Every four years a comprehensive report is produced by UNEP on substances that deplete the ozone layer and the Montreal Protocol.

Annex 1

Montreal Protocol: non-Article 5 countries

1. Andorra
2. Australia
3. Austria
4. Azerbaijan
5. Belarus
6. Belgium
7. Bulgaria
8. Canada
9. Cyprus
10. Czech Republic
11. Denmark
12. Estonia
13. European Union
14. Finland
15. France
16. Germany
17. Greece
18. Holy See
19. Hungary
20. Iceland
21. Ireland
22. Israel
23. Italy
24. Japan
25. Kazakhstan
26. Latvia
27. Liechtenstein
28. Lithuania
29. Luxembourg
30. Malta
31. Monaco
32. Netherlands
33. New Zealand
34. Norway
35. Poland
36. Portugal
37. Russian Federation
38. Romania
39. San Marino
40. Slovakia
41. Slovenia
42. Spain
43. Sweden
44. Switzerland
45. Tajikistan
46. Ukraine
47. United Kingdom
48. United States of America
49. Uzbekistan

Revision history

Date	Change summary	Reason for change	Approved